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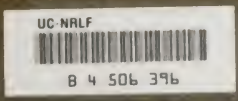

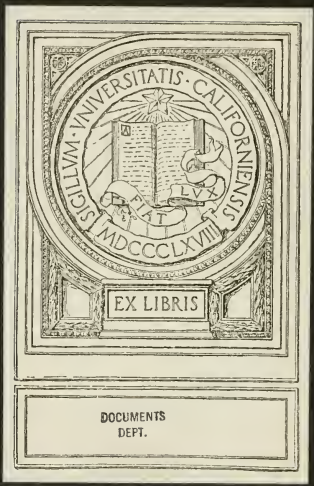
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The Causation and Prevention of Tri-nitro-toluene (T.N.T.) Poisoning.

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The Causation and Prevention of Tri-nitro-toluene (T.N.T.) Poisoning.

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The enquiries of which Dr. Moore gives an account in the present Report originated in a request made in August, 1915, to the Applied Physiology Department of the Medical Research Committee by the Medical Inspectors of Factories at the Home Office, for assistance in the investigation of the toxicology of tri-nitro-toluene.

In the previous months these Inspectors, Dr. Legge and Dr. Collis, had their attention called to the occurrence of serious symptoms leading to toxic jaundice among workers engaged in the manufacture of T.N.T. or in its manipulation for filling munitions of war. The first recorded death from this cause occurred in the manufacture of T.N.T. in February, 1915, and from its use in a filling factory in August, 1915. But already in a filling factory in July, 1915, a case of toxic jaundice had been reported. The symptoms of poisoning were closely akin to those which were then being reported as due to exposure to the fumes of tetrachlorethane, used as a constituent of varnish applied to aeroplanes. This coincidence in time of the two forms of poisoning made it natural then, to look upon the inhalation of the fumes or the dust of T.N.T. as a possible cause of this new and unexpected danger at the filling factories, in spite of the fact that the path of entry to the body in the most familiar examples of poisoning from the industrial use of nitro-compounds was well known to be the skin.

The rapidly increasing use of T.N.T. at that time made the position one of grave anxiety, and had it not been for the preventive measures, based on previous knowledge and experience of the nearest analogies, which were then promptly advocated by the Home Office, the mortality from this poisoning, which advanced during 1915-16 until the autumn of 1916, when it reached its greatest height, must have been far higher. In July, 1915, the Home Office had warned the factories that T.N.T. might be absorbed through the skin, or by the inhalation of dust and fumes, and had recommended accordingly those precautions should be taken against both avenues of entry.

The work begun in these circumstances under the direction of Dr. Moore at the Committee's Applied Physiology Department had for its immediate object the settlement of the question of the mode, or modes, of entry of the poison, with a view to its effective prevention. The enquiries of Dr. Moore and his colleagues were only rendered possible by the supply of materials for laboratory experiments and by facilities obtained for him at the factories by the Home Office, acting with the ready co-operation of the occupiers and of the Ministry of Munitions. For the opportunities so provided, and no less for the assistance of managers and other officials at the factories by their practical help and by criticism, the Committee are greatly indebted.

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These investigations show how far the measures adopted in the original emergency were correct; it was inevitable that practice and experience, illuminated by scientific enquiry, should have called for their modification and progressive improvement. In the autumn of 1916, the Minister of Munitions appointed an Advisory Committee to consider and advise him upon the progress of knowledge and its application in the organising of preventive work at the factories. This Committee, upon which the Medical Research Committee were directly represented, framed and recommended the Code of Rules which during the present year has been imposed upon all factories concerned in the manipulation of T.N.T. They have been in close touch throughout with Dr. Moore's work and with other supplementary enquiries, and the regulations they were led to recommend were in very large part either based upon or fortified by the investigations now to be described.

It may be mentioned here that the number of cases of toxic jaundice from T.N.T. given in the Returns of the Home Office for the months of July and August, 1916, show 53 cases, including 13 deaths, as compared with 17 cases (7 fatal) in the corresponding months of 1917, though the number of the workers exposed in the present year to risk has been far greater than in 1916. Accompanying the cases of jaundice there has also been an unmeasurable volume of minor illness, standing presumably in some high direct ratio to the number of serious cases. The latest Returns show that the number is being kept down—and especially the number of fatal cases—and there is now good ground for believing that when all factories have reached the standards attained by the best of them from this point of view, T.N.T. poisoning may become almost unknown. The results already obtained must be regarded as a striking testimony to the value of close co-operation between research work on the one hand, carried out not only in the laboratory but also in the field of its practical application, and administrative action on the other.

While the experimental analysis of the paths by which T.N.T. may enter the body, and the new tests which have been devised for tracing its elimination in changed form, have greatly aided the successful measures of prevention, it will be seen in the following pages that much still remains to be discovered with regard to the detailed nature of the complex toxic effects of T.N.T. or of its derivatives, when it has once gained access to the system. As in the case of other nitro-compounds, an immediate and obvious result of T.N.T. absorption, whether through the skin or otherwise, is a chemical change in the hæmoglobin of the red blood corpuscles and a consequent damage to the oxygen-carrying functions of the blood. This shows itself by a darkening of the blood colour and in a pallor or

duskiness of the skin with blueness of the lips ("cyanosis"). These chemical signs are accompanied by symptoms illustrating the deficiency in oxygen transport, and the consequent oxygen famine, which is intensified in time of need, as is shown by breathlessness or air hunger upon exertion. At least within wide limits, this condition is one from which the body can rapidly recover. If the fresh entry of poison be prevented, what is present is eliminated and the red blood corpuscles are rapidly restored by reversed chemical change and by fresh production, or both, to the normal, and this process is greatly aided by access to abundant fresh air.

Cyanosis is an abnormal condition, but by itself it does not kill. The fatal results of T.N.T. poisoning have been due to two other pathological conditions. The most common has been a destruction of liver substance, overcoming the efforts of the body towards repair, and the outward sign of this is given by the escape of bile-pigments from the liver to the general system. These pigments give the yellow tinge to the skin and other tissues to which the name "toxic jaundice" of this disease has reference. The second and rarer form of fatal ending has been the so-called "aplastic anæmia," in which the blood forming organs fail in function and a progressive loss of the blood elements results. At present both "toxic jaundice" and "aplastic anæmia" are incurable and rapidly fatal diseases when once established. It is of the highest importance, then, to detect the earliest possible indications of their beginnings, with a view to prevention, and the question of early detection, especially of toxic jaundice cases, has been one of the chief practical problems during the past year.

It will be seen in the following pages that Dr. Moore regards both toxic jaundice and fatal anæmia as secondary results of the same action of the poison as that which causes the symptoms of cyanosis. It is reasonable, *a priori*, to regard with him both these diseases as the culminating effects of strain thrown by the conditions of cyanosis upon the liver and upon the blood-forming organs respectively, of which both are concerned in the maintenance of normal blood conditions, and he develops this line of argument fully in his Report.

Upon present evidence, however, it is possible to hold, and some do hold, that while the cyanosis due to T.N.T. poisoning is that characteristic of many nitro-compounds, yet T.N.T. or some of its isomeric impurities, or one or other of its derivatives in the body, may have a toxic action upon the liver cells, and may produce toxic jaundice, independently of, or even without, a concurrent cyanosis. Those who hold this view lay stress on the independent variability in the degree of cyanosis on the one hand and of jaundice on the other. Cyanosis is the inevitable and invariable result of T.N.T. poisoning in experimental animals, while toxic effects upon the liver have been very rarely produced. In dinitrobenzene poisoning, of which there is long industrial

experience, while cyanosis is invariably produced, toxic jaundice is practically unknown. In the T.N.T. factories, again, while there have been many cases of severe and prolonged cyanosis upon which toxic jaundice has not supervened, many of the most serious cases of toxic jaundice have begun apparently without cyanosis, and it has been specially notable that toxic jaundice has occurred in many, if not in most, cases after a very short period of exposure to risk, and therefore after a necessarily short history of cyanosis.

It is plain at all events that we are not yet possessed of definite knowledge as to the precise modes of action of T.N.T. in the body, apart from its capacity as a nitro-compound to produce cyanosis.

Nevertheless, all will agree with Dr. Moore that, as a matter of practice, evidence of cyanosis should be taken as a danger-signal, and as an indication for immediate cessation from exposure. This principle has, indeed, been laid down for the guidance of medical officers at all the factories from the beginning, and it has been progressively adopted in routine practice. Whether or not cyanosis and toxic jaundice are merely separate signs of one and the same toxic action, or whether they represent different and independent poisoning processes, all may agree that the existence of cyanosis shows certainly that the poison is being absorbed, and that at all events the liver and the bone marrow, no less than the blood, are now, as Dr. Moore says, in the "danger zone."

Further studies of the detailed toxicology of T.N.T. and of some of its derivatives are now in progress on behalf of the Committee, and it is hoped that these may solve some of the problems still unsettled. Fuller knowledge of this toxicology must be expected to lead to definite advance in curative treatment, but the progress of preventive measures may perhaps remove in the near future, as we may now hope, any need for its practical application.

30*th October*, 1917.

Medical Research Committee,
15, Buckingham Street,
Strand, W.C. 2.

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The Causation and Prevention of Tri-Nitro-Toluene (T.N.T.) Poisoning.

AN ACCOUNT OF RESEARCHES BY THE STAFF OF THE APPLIED PHYSIOLOGY DEPARTMENT OF THE MEDICAL RESEARCH COMMITTEE

REPORTED BY

BENJAMIN MOORE, D.Sc., F.R.S., M.R.C.S., L.R.C.P.

I. Introduction.

This report is intended to furnish a historical and scientific account of inquiries commenced in August, 1915, when our attention was drawn by Dr. E. L. Collis, of the Home Office, to the earliest known cases of poisoning amongst workers manipulating T.N.T. in the factories.

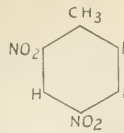
The work was carried out for the first year by the writer, assisted by Mr. T. A. Webster; in May, 1916, we were joined by Dr. G. A. Wyon, and the prosecution of the work in factory and laboratory has occupied our attention since then.

(a) *Constitution and Properties of T.N.T.*

The material known commercially as T.N.T. is mainly composed of one of the three isomeric tri-nitro-toluenes, being that one called symmetrical tri-nitro-toluene because the three nitro groups (NO_2) are symmetrically arranged on the toluene nucleus. In the commercial product there are present only insignificant amounts of the two asymmetrical isomers, and a variable percentage of mono- and di-nitro-toluenes according to the degree of nitration and purification; there are also small amounts of nitrated methanes and other substances. The question of the relative share of these various impurities contributing to the production of the toxic effects on the workers has been gone into fairly fully by ourselves, and is now being still further investigated by other observers, for the pharmacological action of these substances possesses an interest in itself. It is sufficient to state here that we found none of these associated impurities possessed high enough toxicity to account for the effects seen amongst the workers, that workers on *pure* T.N.T. showed all the symptoms, and that similar toxic effects resulted in animals treated with pure T.N.T.

The symmetrical tri-nitro-toluene is the main constituent of the high explosive T.N.T. because it is that one formed when

toluene ($C_6H_5CH_3$) is nitrated fully in the well-known processes with strong nitric acid; it is assigned the formula :—



Symmetrical Tri-nitro-toluene or T.N.T.

The pure product is a hard crystalline powder, the crystals when thrown out from hot alcohol form long glistening needles. When free from impurities it is almost odourless, unless fine dust of it be stirred up to irritate the nasal mucous membrane, and the smell of commercial samples of lower grades is almost entirely due to lower products of nitration and other impurities.

It melts at 82°C., and sublimes slowly at this temperature. At atmospheric temperatures its vapour pressure is very low, and practically none, as we show below, is contained as vapour in factory air.

This substance was perfectly well known as a high explosive internationally, and was used fairly extensively for mining purposes, long before the war.

It was not only used alone, but in mixtures with diluents, and the varieties known as "Amatol" are of quite pre-war days.

It owed its successful introduction in the times of peace as a blasting powder to two excellent properties of such an explosive, viz.: (1) its high stability, so that it could be relied upon not to go off spontaneously, but remain stable until intentionally detonated; and (2) its low toxicity to human beings, so that it did not induce illnesses and poisonings amongst those employed in its manufacture and after manipulation.

In spite of all that has happened since, these two properties it must be admitted to possess in a high degree. As regards stability it may be hammered or turned up in a lathe, and as regards toxicity, any pharmacologist would agree that the toxic and lethal doses shown below are relatively enormous doses.

Paradoxical as it may sound, it is these two *safe* properties which have conduced to the greater part of the mischief.

Used aright they may be made to conduct us to relative safety, both from toxic effects and from fires and explosions; but, treated as absolute safeguards, they may lead to T.N.T. poisoning on the one hand, and to fires followed by explosions on the other.

When once it is realised that it is a low-grade chronic poison with which we have to deal, and the channel of entry to the body is known, and the earliest symptoms of its presence in toxic amount recognised, all the means are then at hand for practically sweeping out T.N.T. poisoning, and that goal we are now rapidly approaching.

Also, when it has become recognised as it has now how inflammable it is once any ignition has occurred, and that thereafter the high stability safeguard disappears, a proper objective is supplied to means for prevention of accidents, for then reliance on high stability is replaced by reliance on scrupulous cleanliness, and risks fall to a minimum.

Thus many of the means of prevention are identical for both types of danger, and, in addition, as will presently be shown, the industry and ingenuity called forth for the invention of the necessary safeguards eventually lead to quicker and better methods of labour, yielding the reward of increased output by a diminished army of munition workers exposed to the poison.

The innocent character ascribed to T.N.T. prior to the enormous increase in its manipulation caused by the war, may be gathered from the following quotations from the classical article of Robert Prosser White, the chief authority on the toxic properties of such bodies, in the *Lancet*, August 31st, 1901, and in a later work, "Manufacture of High Explosives":

[redacted]

[redacted]

[redacted]

[redacted]

The above quotations, especially the sentences which we have italicised, illustrate the aspect of expert opinion on the toxicity of T.N.T. previous to the war. The experimental work upon which it is based is, we believe, sound, for we have tested the toxicity of dinitrobenzenes as well as dinitrotoluenes, trinitrotoluene, and other allied explosives for the Department of Explosives Supplies, and can confirm Prosser White that dinitrobenzene is more poisonous than trinitrotoluene, and that both dinitrotoluenes and trinitrotoluene are practically innocuous in such doses as he administered in this early work.

(iv) *Channels of Absorption into the Body.*

As regards the channels of absorption of these nitro explosives in general, there are some desultory observations and remarks in the pre-war period by both our own and German workers. Thus F. Curschmann,* in a general article on the toxicity of

* Die Vergiftungen bei der Arbeiterkrankheiten und der Fabrikhygiene (Lehrbuch der Arbeiterversicherungsmedizin. Nitro- und Amido-Verbindungen. Pp. 1–15. Leipzig, 1913. J. A. Barth.)

aniline and nitro-derivatives, draws attention to the importance of the skin as an absorptive channel, and says this throws light on several cases of obscure poisoning, which were doubtless due to skin absorption.

Prosser White also points out that poisoning with nitro-derivatives may occur after the most careful attention to use of respirators and ventilation of factories from dust and fume has been applied, because of the nitro-compounds getting upon the skin of the operatives.

Neither observer says anything of the substance of our immediate quest, tri-nitro-toluene, which then enjoyed a most innocent reputation, and no one seems to have made an attempt to determine the peril, if any, from inhalation of its dust and fumes, up to the time when cases of poisoning first came into notice and the preventive measures were directed against such inhalation. Such preventive measures were taken as had been proved effective in preventing other proved inhalation poisons, such as lead or silica dust.

The breathing of operatives was incommoded by the use of respirators even in places where the air was almost guiltless of dust, and time, labour and money were expended on elaborate systems of fan ventilation in factories situated in open country sites where the natural air circulation seemed to us excellent.

This is an object lesson in the value of getting at root causes, for when the thoughts for prevention are thrown into fresh channels and the essence of the problem becomes that of keeping skin, and especially the hands, clean, not only may there be the saving of thousands of pounds which would otherwise be spent on useless preventive appliances, but attention is turned to clean and mechanical methods of pouring and filling, to finding out how the numbers of hands necessarily in contact can be diminished, to the introduction of impermeable preparations for keeping the skin clean, and to finding out methods for testing before their employment those individuals who have susceptible skins.

In the beginning of our inquiry, to test the "fume" theory, different species of animals were exposed in a respiratory chamber for days to the strongest fumes which could be produced by heating up crude T.N.T. well above its melting point in a flask and, by means of a pump, aspirating air through it and the respiratory chamber containing the animals. So strong were the fumes that crystals of T.N.T. appeared on the outlet tube. Guinea pigs and white rats exposed to this treatment did not show any effects.

Next, rabbits, guinea pigs and white rats were taken down to Factory W, and by kind permission of Major O'Reilly and Mr. P. J. Hincks, manager of the Danger Buildings, these were suspended in cages over melting pans containing molten T.N.T. in a position where exposure to fumes was worse than any workman endured, and constant during the whole shift,

not for small intervals as in the case of the workman who has to throw in occasionally fresh quantities of T.N.T. to melt.

These experiments were repeated several times and kept up for months; the animals grew up, waxed fat, and reared families. We have never seen finer, larger and fatter white rats than these of one set after six months' exposure over the Woolwich melting pot. On the other hand, further experience has shown us that the excessive exposure does give enough absorption to affect kittens and cause them to become cyanosed. The cat is an animal very sensitive to T.N.T.

Next by the kindness of the management here we were provided with a means of separating the air from over the molten T.N.T. in the pans, through a system for collecting "fume" devised as follows: A large funnel was hung mouth downward right over the centre of the large double-jacketed boiler in which crude T.N.T. was melted by steam. This was connected with a long wide glass tube which had at one point a glass-wool plug to catch any dust of ammonium nitrate or condensed T.N.T. vapour. This wide glass tube passed to another outside the hut, and as the experiment was carried on for three weeks round about Christmas, 1915, the transition from the hot air inside to the cold outside induced to throw down any T.N.T. not deposited on the funnel and tube within the warm hut. There were a few delicate crystals of T.N.T. in the tube at the end of the experiment, but the main amount paid that, as will be seen below, not very much was found on the inner surface of the funnel, on the first glass tube and in the glass-wool plug.

To make sure of complete absorption, during the last period of the experiment consisting of an entire shift, two U tubes were placed after the glass tubings mentioned above, and these were surrounded, to cool them thoroughly, with carbonic acid snow. The whole system was attached by tubing to a gas meter, and from this in series to a Bunsen's water suction pump. The air was separated away from over the molten T.N.T. at a rate of about double that at which a man would breathe.

The only thing which condensed in the U tube kept at the temperature of carbonic acid snow was a few drops of slightly acid water condensed from aqueous vapour, which were injected into a rabbit without any obvious result.

The air was then separated for three weeks constantly through the apparatus. At the end of the experiment, only T.N.T. and ammonium nitrate could be found in small quantities in the system. This was thoroughly washed out with ether, the ethereal solution dried and the extract weighed and found to be about 0·1 gramme. By the usual test and a melting point determination a part of this substance was shown to be T.N.T. The remainder, being almost the whole of the 0·1 gramme, was then fed at one dose to a rabbit without producing any observable toxic effect, a result in keeping with our other observations on the direct effects of feeding T.N.T. to animals.

The apparatus had been working for a period of 40 shifts, drawing air through at double the rate of human respiration, so that if we wanted to calculate the amount breathed by a workman during a shift we should have to divide 0·4 grammes, or 400 milligrams, by 80, so obtaining 5 milligrams. The inhalation of this amount can hurt nobody; it corresponds fairly well with what we later obtained by even more precise methods of experimentation in workshops, both at Factory F. and elsewhere.

The first case of poisoning which seemed to be attributable to T.N.T. occurred early in 1915, and in the summer of 1915 there was the first fatal case.

The reason for believing at this period that "fume" rather than "dust" was the causative agent was that these earlier cases appeared exclusively amongst workers with hot molten T.N.T.; this occupation was not, on the whole, as dusty as other occupations such as filling "exploder bags" or "hand-stemming" with dry powder where as yet no cases had appeared.

A few months later, however, there occurred the death of a worker filling "exploder bags" with *pure dry* T.N.T., who had never been near molten T.N.T.

Widening our views somewhat, we then asked, is this simply another form of inhalation of fumes, or of very fine particles of T.N.T. suspended in the air? Surely, in the case of a substance with so high a boiling point as T.N.T. the fumes would soon pass from vapour into fine particles in solid form.

So, we set forward on that basis, recommending in factories all possible devices for dust and fume prevention or removal, and on the laboratory side, inventing an apparatus in which, by knocking and blowing a suspended bag containing T.N.T. powder, an atmosphere containing fine dust could be blown at the head of an animal. Rabbits exposed to this treatment for an hour daily for weeks showed no signs of poisoning.

It also struck us at this point as peculiar from the workshop side that in the incorporating and grinding mills of certain factories where the amount of dust was *enormously* greater than elsewhere there had been no severe cases and very little minor illness.

Two other disconcerting cases of T.N.T. jaundice, one of them fatal, dropped in upon our train of thought about this period. One was the case of a woman who only stencilled shells, it is true in the same room as tamping or stemming was done, but much more remote and less exposed to the dust. The second case was more perplexing still, being that of a woman who merely put waxed blocks containing T.N.T. *made at quite another factory* into shells, where there seemed no possibility of dust or fume; later on a second toxic jaundice case occurred on this type of work where only waxed blocks were handled.

Parallel to these events many laboratory experiments had shown the low toxicity of T.N.T. administered by the mouth to

the majority of types of laboratory animal, such as rabbits, guinea pigs and white rats. Cats and dogs relieved themselves by vomiting up the dose, but were distinctly more affected than the rodents.

A sample of these laboratory experiments, selected from many of variable length, on account of prolonged duration, must here suffice. (See also Appendix E.)

Two rabbits were each given 0·1 gramme (100 milligrams) of T.N.T. with their food *daily* except Sundays, from October 15th till December 31st, 1915; both of these animals not only survived, but flourished and put on weight.

Only when such doses as half a gramme (500 milligrams), enormously disproportionate to anything which an operative could swallow at work, as shown below, were given by the mouth to a rabbit, was it possible, and then only after three or four rapidly repeated dosages, to kill the animal.

In many animals of several species we have patiently tried to reproduce typical T.N.T. jaundice by repeated sub-lethal doses, but in only three sub-chronic cases did we obtain lesions of the liver pronounced by the pathologist to be microscopically similar to early T.N.T. poisoning. This is not remarkable, for it is notoriously difficult to obtain experimentally the lesions of chronic poisoning—thus lead poisoning as seen in operatives has never been reproduced in laboratory experiments, and, so far as we know, no pharmacologist has ever produced alcoholic cirrhosis of the liver by administration of the drug to animals. These three positive results compared with the total number of experimental animals are not a less proportion than the number of cases of toxic jaundice in workers compared with the total numbers of workers on T.N.T. Our thanks are due to Dr. Hubert M. Turnbull, Director of the Pathological Institute, London Hospital, for undertaking for us the pathological investigation of the organs of these animals, as well as those taken from several cases of human T.N.T. poisoning.* The attempts are still being continued, but it must be remembered in this connection what a small proportion of T.N.T. operatives ever show typical lesions of liver and kidney so characteristic of fatal poisoning.

During the year 1916 the output and manipulations of T.N.T. increased enormously, and from about March in that year the number of cases began to increase to reach a maximum in August and September.

It was during a visit to a small factory H.W.C. near London, in company with Dr. Legge and Dr. Wyon in August, 1916, that it first occurred to the writer that the trouble might arise through the skin.

The occasion was due to a case having occurred in the pressing of T.N.T. pellets from dry pure T.N.T., and a visit showed that this work was carried out in small isolated sheds under almost open-air conditions: there was no appreciable dust in the air, no

* See Proc. Roy. Soc. of Medicine, 1917, X 47.

smell of T.N.T. fumes, no ammonium nitrate, or molten T.N.T. But the hands of the workers were deeply stained and oily, and a test for the presence of T.N.T. in the urine, a test which one of us (T. A. Webster) had just then evolved, indicated the presence of T.N.T. in their urine. Here, then, were operatives working under conditions practically free from dust and fumes, but with hands saturated with oil and T.N.T. Webster's test showed that the T.N.T. was passing into their bodies, and T.N.T. illness had been noted amongst them.

(iii) *Fate of Absorbed T.N.T.*

As Webster's test indicated the presence of modified T.N.T. in the urine, it formed a most important engine of research for us in our future work, and it is more in this direction than as a diagnostic or prognostic sign that it has its significance.

Our attention had been directed from an early period in the research to the fate of absorbed T.N.T. in the body; we had sought for its presence in the organs, fæces and urine of poisoned animals, in the urine of patients suffering from toxic jaundice, and in the organs of persons who died from the poison.

With the exception of (1) the organs of white rats which died after taking heroic doses of T.N.T. from acute T.N.T. poisoning, (2) the fæces of rabbits which had received large doses by the mouth, (3) the urine of white rats allowed to walk about in the T.N.T. powder, we had not been able to trace the T.N.T. in the body.

The drug behaves differently in different animals; if the white rat be given a dose by the mouth, or be allowed to walk about in a box smeared over with T.N.T. dust, the urine shortly thereafter acquires without any treatment that pink colour which is shown by T.N.T. solutions after treatment with alkaline alcohol. This is the only animal experimented upon by us in which the colour reaction appears in the urine straight away; the urine in these animals is pink even in the bladder. It is interesting to speculate what the consequence would have been had the human organism behaved like that of these rats, for then the majority of our tens of thousands of T.N.T. workers would be passing a bright pink urine.

In the case of the rabbit and the human being the colour may be shown in the urine by the procedure presently to be described; in the cat we have failed to obtain it *even by this procedure.* Another substance related to T.N.T. is detectable in their urine, giving quite a different colour reaction. This difference may perhaps be related to the higher susceptibility of the cat.

Webster's Test. Although T.N.T. and also the modifications formed from it in the body are easily soluble in ether, yet, if the urine containing the excreted compound be shaken up with ether, and the ether be separated and tested with alkaline alcohol, no colouration results, showing that the ether has failed to remove it. But if the urine be mixed with an equal volume of 20 per

cent. sulphuric acid solution,* and again shaken out with ether, the ether separated and washed free of acid with water, and then tested with alkaline alcohol, the pink colour characteristic both of T.N.T. and a reduction derivative of it formed in the body appears.

When the amount of T.N.T. in a sample is large, giving rise to a suspicion of contamination of the urine by contact with skin, hair or clothing, the urine should be extracted first with ether without adding any acid; if a pink colour then appears on adding alkaline alcohol, it is due to *T.N.T. of contamination*. But the specimen need not be thrown away, the first washing with ether without acidifying has removed the *T.N.T. of contamination*; all that is necessary now, to disclose the modified T.N.T. which *has passed through the system*, is to acidify as directed above, shake out with ether again, separate the ether, and test with alcoholic potash.

Exact details and quantities for carrying out the test have already been circulated to the factories. It is sufficient for the purposes of this paper to state that, although no accurate way of making the test quantitative is known at present, each observer can agree upon an empirical standard for himself for judging various degrees of intensity.

Having found this test for the passage of T.N.T. through the body of the rabbit on time was lost in determining whether it applied to human beings, by obtaining samples from T.N.T. workers at various factories, and by taking doses of T.N.T. ourselves. Fortunately, it was found that the human being absorbing T.N.T. *does excrete it in the modified form*, and so we had at our disposal a powerful tool to our research, of which we at once proceeded to make full use.

Before taking up the tale of these again, a few words may be devoted to the changes which T.N.T. undergoes in the body of the rabbit, premising that so far as the extent to which these are similar to the changes in the human being, but different from those in cats or white rats, which again differ from each other.

The changes were studied in the rabbit's urine, because of the difficulties of collection of human urine at works and the variations in the degree to which they are loaded with T.N.T.

The rabbit is a highly resistant animal, as can be by feeding on T.N.T. its urine can be loaded with T.N.T. derivative and a sufficient amount separated for analyses and identification.

The urines of practically all workers in T.N.T. contain this substance, but in some there is only a minute trace, in others an intense reaction, and there may be a high reaction where there is no sign of T.N.T. illness or illness with only a moderate degree of reaction.

* 2 c.c. to 100 c.c.

This work has been carried out by Mr. T. A. Webster and Dr. G. A. Wyon—Mr. Webster undertaking the chemical side, and Dr. Wyon the physiological preparation and tests on the animals. This work commenced independently has been continued under the supervision of Dr. H. H. Dale, F.R.S., and Dr. Barger in the Bio-chemical Department of the Medical Research Committee, at the Lister Institute, and our warmest thanks are due to our colleagues of this department for the special knowledge which they have so freely placed at our disposal.

The researches will form the subject of a special memoir, so the proofs and details of experimentation need not be given here. It may, however, be said that the solution of the problem is now practically complete, and that the interesting changes undergone by T.N.T. in passing through the body are as follows :—

The colour obtained when T.N.T. urine is treated as in Webster's test is not due to T.N.T. itself, but to a substance formed from it by the reduction of one of the nitro-groups. This substance is 2 : 6 dinitro, 4 hydroxylamino-toluene. It is excreted in the urine, conjugated with glycuronic acid, from which it is liberated by the treatment with acid.

The fact that the tri-nitro-toluene after the preliminary reduction is finally excreted as an ester of glycuronic acid is of interest because glycuronic acid shares with the sulphonic esters, or the so-called ethereal, sulphates, the task of removing from the body in innocuous form such a large number of poisonous substances. These poisons may either be formed autogenously in the body by physiological or pathological processes, or obtain admission by some channel from without the body.

Examples of the first category are the phenolic compounds such as indol and skatol, which are formed in putrefactive processes in the large intestine. When unpaired they are highly poisonous, but if conjugated with glycuronic acid they are harmlessly excreted as esters, and are found in this condition in the urine. The number of drugs which after administration are excreted as glycuronates is legion, and one of the chief methods for obtaining glycuronic acid is the daily administration of such drugs to a resistant animal. For example, camphor may be administered for this purpose to rabbits. Amongst drugs which appear conjugated with glycuronic acid in the urine are chloral hydrate, phenol, resorcin, synthetic febrifuges, menthol, camphor, sandal oil, β-naphthol and morphine.

A most interesting example of the formation of a glycuronic ester is that recorded by M. Jaffé (*Z. f. physiol. Chemie*, Bd. 2, 1878, S. 47), which occurs when ortho-mono-nitro-toluene is administered to dogs. The para- and meta-isomers do not yield such esters, but conjugate with glycocoll and with hippuric acid.

In view of the extreme tolerance for tri-nitro-toluene of herbivora, as contrasted with carnivora, it is noteworthy that amongst the large number of substances which are rendered less noxious in the body by conjugation with glycuronic acid, many can only be so united by herbivora, while others can be dealt with in much greater quantities by the herbivora than by the carnivora.

Man with his mixed diet stands in an intermediate position.

Various diets yield varying amounts of glycuronates or glycuronate esters utilizable for countering these poisons, and it would appear of importance to provide for all workers on toxic nitro compounds of benzene, phenol or toluene, a diet which will yield a good supply of glycuronates. Such a diet should contain plenty of fresh vegetables and fruit, and be, in fact, arranged on the principles of anti-scorbutic diet.

There may be a struggle between the poisonous aromatic derivatives from without, such as trinitrotoluene, and those formed autogenously in the intestine, such as phenol, cresol, indol, and skatol, for the available glycuronic acid which the organism can manufacture from the diet. If the supply is insufficient for both purposes, there will be free poisons either those of the organism's own formation or of the intestinal type, which will then attack those tissues and cells of the organism for which they possess the highest selective affinity or chemical combination. This occurs when the poisons attack the blood constituents and blood-vessels, red bone marrow, and hepatic parenchyma.

It is important to note the contrasted lesions certain symptoms of T N T poisoning, such as purpura hemorrhagica, and blood crises. In a majority of cases of T N T poisoning purpuric areas are found either subcutaneously or in the mucous tissues and serous membranes, but are usually overlooked by other more striking changes. In three recent cases, however, purpuric eruptions were the most characteristic feature, and in one case there were copious hemorrhages from spongy gums, and the teeth were loosened. This case of T N T poisoning and scorbutic treatment — but here it must be remembered that the patient left free to the hand for lack of appreciation will obtain nourishment different from that which would be furnished in the daily ward ration, a fatal amount of ascorbic acid may have been found from cells, probably the hepatic ones, which persist in the organism.

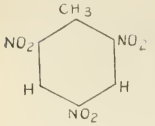
Additional weight is given to these observations by the conclusions stated in a recent paper by Iskovitch (Iskovitch Zonen, Bl. et Inst. P. 1916), in which a sublimate poison, viz., mercuric bichloride, administered to rabbits in order to produce a supply of glycuronic acid from the tissues for other purposes. It was found that when a single dose of 0.0005 gm. of menthol was given daily the yield of urinary glycuronic acid was first represented mainly by the phenol in the urine (phenolsäure), and probably for all the rabbits had been more completely free of urea, without any trace of free glycuronic acid; but when the phenol content in the urine was decreasing, presumably by the onset of the poisoning, the rabbits began to lose their appetite and especially their urine-rates were put on a daily measuring urine examination. When free glycuronic they were able to have the control dosage, although the amount of menthol given was always sufficient to kill. The method is one of possible use in the study of the relative resistance to poisons of different individuals and species of animals, although the present writer appears to have taken issue with the importance of the observations, though it claims the credit of first to introduce reasoning in such a form of poisoning and has used a hearing on the disease due to the drug poisoning and one is left confident. In both diseased states there is a considerable profound metabolic disturbance, and one point of agreement is the conjugate to act in urinary tissue.

The hydroxylamine compound, on boiling with dilute hydrochloric acid, is converted into 2 : 6 dinitro, 4, aminotoluene and 2 : 6 dinitro 4 acetaminotoluene. Owing to the great solubility and sparing solubility in organic solvents, the latter component is easily isolated and identified.

It has been isolated from the urines of rabbits and a monkey infected with T N T ; also from human urine after the oral administration of T N T , and from the urine of workers in T.N.T factories. It is not present in the urine of rats poisoned by administration of T N T.

The relationship of these two derivatives to the original trinitro-toluene are shown by the following structural formulæ :

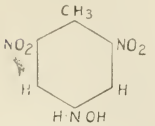
Symmetrical Tri nitro-toluene T.N.T.



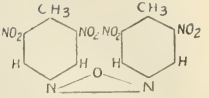
United in urine to another substance not derived from T.N.T. When freed and treated with alkaline alcohol gives pink colour (Webster's test).

Formed synthetically by reduction of T.N.T.

2 : 6 Dinitro—4, hydroxylaminotoluene.



Azoxy-compound



Azoxy-compound 2 : 6 dinitro, 4, azoxy-toluene formed by condensation of previous compound by acid or alkali. Gives permanent blue with alkaline alcohol. Both urinary derivative and synthetic ones give this test.

In the free condition the hydroxylamine derivative is not innocuous ; in fact, experiments on animals show that it has about treble the toxicity of T.N.T.

The action upon T.N.T. in the cat (which, like the dog, is much more susceptible than other species of animal) differs from that in the rabbit and man, where the colour tests would appear to indicate identity of action. No pink colouration is obtained when Webster's test is applied after administration of T.N.T. in cats, but instead a yellow colour. This yellow is only obtained when T.N.T. is given. The substance giving the yellow colour has not yet been isolated, but it is hoped as soon as opportunity serves to carry out more experiments on the subject.

Taking up again the historical thread of our progress on the work-shop side of the investigation, we had found that cases of toxic jaundice had now occurred not only amongst workers with molten amatol, but (1) with workers with *pure* dry T.N.T., (2) with dry amatol, (3) with cold waxed block charges, and (4) finally, amongst pellet-compressors where both dust and fume in the air were at a minimum.

The hands of this latter class of workers were oily and deeply stained from coming in contact with *pure* T.N.T. pellets and *pure* T.N.T. on the benches, but there was practically no T.N.T. dust in the air, and no smell of T.N.T. fume. Also, the Webster test showed that T.N.T. was passing in varying degrees through the systems of these workers.

It was this situation which decided us upon making the prolonged and crucial research at Factory F. which, finally, indicated clearly the share taken by the different channels in admitting T.N.T. to the body.

The inception and conduct of this research must now be described, but before doing so, in order to preserve historical continuity, it is necessary to give here some account of a number of peculiar aberrant cases, terminating fatally, the first two of which came under observation between August and September, 1916.

(iii) *Aplastic Anæmia caused by T.N.T. Poisoning.*

One of the earliest of these cases I saw was at Factory W., by the courtesy of Major P. S. O'Reilly, R.A.M.C., senior medical officer, who throughout the whole of these researches has always put himself unweariedly at our service in the midst of his abundance of official duties.

The patient was a man who had been for some months engaged on amatol work, and who had never been known to have been jaundiced, but he had grown progressively worse from anæmia, and when we saw him he looked the picture of *pernicious anæmia*; this was indeed, what his disease was supposed to be in spite of the perplexity introduced by his contact with T.N.T., and also by the fact that he had formerly been a painter.

Blood films were taken, stained, and examined, when the remarkable fact was discovered that none of the characteristic blood changes of pernicious anæmia were present.

The films might have been taken from a healthy person, and in this we were confirmed by Dr. William Bulloch, F.R.S., of the London Hospital, who kindly examined them for us. The only change that could be detected was a certain variability in size of the red blood corpuscles, but there were no nucleated red corpuscles, no poikilocytes and no abnormalities in the white cells.

Dr. Wyon and the writer then went down to Factory W. and made counts of the red blood corpuscles, and also haemoglobin determinations, when the true state of affairs was at once revealed; the number of red blood corpuscles was only 1,200,000 per cubic millimetre and the haemoglobin percentage 30.

The case terminated fatally, and an examination of the organs by Dr. Hubert M. Turnbull showed that the case was, as indicated by the above determinations, one of *aplastic anæmia*.*

Had this occurred solely it might have been doubtful whether it was due to T.N.T., but just a week prior to the making of the blood counts mentioned above, I had been taken by Dr. T. M. Legge to see an exactly similar case of a woman worker on T.N.T. at Watford; there had here also been no clear observation of jaundice, there had certainly been no *marked* jaundice and there was none when we saw her—she had been treated for influenza and then for gastritis. The anæmia was profound, the blood flow on pricking the finger was scanty and thin, not welling up into a drop, but spreading in a thin dark layer over the skin, and it was with difficulty that films were obtained.

* Proc. Roy. Soc. in Medicine 1917. X 69.

These films on examination gave the same result as in the case of the man above, viz., almost normal condition of both white and red cells, with a certain amount of variation in the diameters of the red cells.

Four days after our visit this patient died. On account of default in notification of the death, the post-mortem examination was delayed for four days, and this prevented histological examination of the organs. The autopsy was carried out by Dr. Legge, and the liver was found atrophied, fibrosed, and very shrunken from before backwards in the middle lobe, in the manner typical of so many cases of T.N.T. poisoning. There was no question in our minds that death had resulted from T.N.T. absorption.

There have since been recorded at least four other deaths from this *aplastic anæmia* due to T.N.T. absorption, making six in all.

Quite recently the writer saw at Northwich, under the care of Dr. R. Mainwaring White, a case of a woman munition worker who had worked at a manufacturing chemical T.N.T. plant; there was no jaundice when she was first seen, and we were assured there had been none. It was almost certainly an aplastic anæmia case of milder type. The prognosis was grave, but she is still living, and, we are given to understand, slowly recovering.

II. Researches at Factory F.

(i) *Methods and Results.*

It was this research which gave us the key to the causation of T.N.T. poisoning and thence led on to the institution in logical sequence of means for its prevention.

Observations were made in the workshop and under workshop conditions on the workpeople and on ourselves, and these showed quite conclusively that the all-important channel of absorption is the skin.

It was shown by testing the value of the more efficient respirators that the effect upon the amount of poison passing through the system was almost negligible. Also that when the hands of workers, or our own hands when we carried out the same operations, were completely protected, the amount then absorbed as shown by the urinary reaction dwindled to a trace. In confirmation of these observations, direct analyses of the air of the workshop for the amount of T.N.T. which any worker would breathe during a shift showed that this is so minute a quantity as to be incapable by itself of doing any mischief.

In such workshop investigations there are at any one time hundreds of individuals under naturally arranged experimental conditions unavoidably exposed, and, under the conditions of our research, which were quite different from those of a rapid visit, it was possible by close and continued experience to get accustomed to the appearances of workers suspected of suffering from the effects of T.N.T. poisoning, and to observe with continuity how the minor symptoms led up to the more serious events.

In this manner it was established that the initial effect of the poison is on the blood, producing oxygen-starch, breathlessness, giddiness, nausea, and, as the most objective physical signs, cyanosis and pallor* which could be traced in several cases on to severe toxic jaundice. Fatal results were avoided by promptly turning cases showing the initial symptoms of contact with the poison.

As a result of these continued observations in the factory, we were able in October, 1916, to suggest a typical *facies* characteristic of early T.N.T. poisoning, before the onset of jaundice, and to recommend that detection should be made on these early signs by observers patrolling and observing the workshops.

There is, we believe, good evidence based both upon the statements of factory doctors and on the monthly Home Office Returns, that where this system has been carried out efficiently, the tide of toxic jaundice has shrunk to a small fraction of its former value, and on the other hand in factories where this early workshop detection has not been efficiently carried on there have been deaths from toxic jaundice.

We have some reason to claim that these workshop experiments and observations have led to the saving of life, to the reduction of the volume of minor T.N.T. illness, and so by a saving of labour through the decrease in the numbers of absentees, to results of considerable economic value.

Analyses of the air in the shops combined with the demonstration that only a negligible amount of T.N.T. was swallowed by a worker who did not use a respirator, have freed the workers from the discomfort of wearing respirators and saved their provision. The work has also shown the inutility of permeable cotton gloves, the wearing of which only makes the skin soft, flushed and more permeable. These, with the laudable object of protection, were supplied free to every T.N.T. worker and their use made so far as possible compulsory.

Such results demonstrate the importance of medical research carried out in the actual workshops, and we are greatly indebted to the facilities offered us at Faversham.

It was in August, 1916, while visiting the Anastol Press Rooms along with Dr. T. M. Legge that the factory research was first discussed. Dr. Legge had brought with him a Siebe-Gorman respirator, which is a valved metallic box respirator used by workmen who are employed where there are poisonous fumes or gases in the air. The pure incoming air is brought by a long wide rubber tube from the open air outside, and the expired air is simply breathed out into the workshop through a mica flap valve, opening outwards.

It was a question whether on account of their cumbersomeness from weight and tube attachments these respirators could be worn as a daily routine by working girls for an eight hours'

* Almost similar effects due to the explosive dinitrobenzol, leading to many deaths, are recorded by French observers.

shift, but it was thought feasible that we might get a selected number of the girls to wear them for some days, while daily analyses were made of the urine by Webster's test in order to determine how much T.N.T. was really taken up by the mouth and nose.

It was pointed out by the writer that the amount of T.N.T. dust in the air at the level of the workers' mouths was very small, as it all fell floorward from the level of the machine moulds, so that while there was plenty of dust (at this period) on floor, benches, and the girls' dresses, very little dust settled on ledges above their heads. These ledges, we were assured, had not been dusted for some time.

This contention as to the small amount of dust in the air was not admitted by others present, who appealed to the bitter taste in the mouth and the irritation of the nostrils. It was accordingly determined to make analyses of the air for dust and fumes at the level of the workers' mouths with the results shown below.

The process employed in this factory consists in compressing the T.N.T. powder into large pellets. Two girls work at each machine, one measuring or weighing with ordinary scales, the charge of powder taken from a box-full alongside, and tipping it into the mould, the other girl manipulates the machine, takes the moulded pellet, which has always some loose dust about it, out of the mould with her hand and places it in a box.

The writer asked several girls to remove the cotton gloves with which they were supplied, and found the powder inside caked in the creases of the skin in many cases, and quite wet from perspiration. The skin of the hand was in many cases soft, and the skins of all the hands were a deep orange colour. It was evident that the gloves were perfectly useless as a means of keeping the powder off the skin; indeed, on the contrary that they were probably harmful in making the skin soft and moist, and holding the powder to it like a poultice cloth.

Our suspicions of the dust and fume theory had already been aroused, and the importance of the skin channel presented to our minds at our visit to H.W.C. (page 15) a few weeks previously; here seemed to be more evidence pointing in the same direction.

It was determined therefore that while one set of girls were protected as completely as possible from dust and fume swallowing or inhalation by respirators, and not otherwise interfered with; another set, or some of ourselves, should take the risk of dispensing entirely with respirators so that we swallowed as much as was available of dust and fume while actually working, but should have our hands protected as completely as possible with rubber gloves, and other means, to keep the T.N.T. off this most important part of the skin where the powder is rubbed in during the process of labour.

The Webster test of the urine was to be made as quantitatively as possible for the two sets of workers—so that a good idea might

be gathered not only of whether the poison entered by one or both of these channels, but also some estimation might emerge as to their relative importance.

Dr. Legge approached the directorate of the factory, who readily granted permission for the research to be carried out, not only so, but they placed a small well equipped laboratory in the grounds adjacent to the factory entirely at our disposal and incurred a considerable expenditure upon chemicals and other materials for our use.

The then managing director, the late Mr. Watson Smith, did everything in his power to facilitate our labours, and our thanks for much valuable help are due to Mr. H. Minter, works manager, and all his staff, and to the workers also, for their patient assistance.

(iii) *Experiments with Six-a German Respirators.*

Two of the small workshops each containing two machines operated by four workers were selected, and fitted up with wide rubber tubes designed to pass from the respirators to the open air outside near the roof. Similar tubes were also arranged to be connected outside to an electric vacuum air pump and inside to an absorbing apparatus for catching T.N.T. dust or fume. This consisted of two tubes in series, the first containing water through which the workshop air could be sucked. When making an experiment the absorbing system was placed at the level of the nose and mouth of the girls serving the powder to the machine, and so favourably disposed as they were for catching any dust which might be in the air. No matter T.N.T. is used in or near these sheds, but several fatal cases of T.N.T. poisoning have occurred amongst the workers in them.

Experiment I in Shop No. 1.—Two girls, V. McC., and L. F., consented to wear the respirators. They wore them all day on Monday, September 4th, 1916, and the greater part of September 5th, but had to take them off on September 6th, 7th and 8th on account of sore faces caused by the pressure of the rubber pads. Advantage was taken of this interruption to establish the intensity of the urinary reaction when no respirators were worn as follows:—

V. McC.	Tuesday, September 5th	B. 2
	Thursday, September 7th	B. 4
L. F.	Tuesday, September 5th	B. 2
	Thursday, September 7th	B. 4

The lower reaction in both cases earlier in the week is due to the partial clearance in the week end.

During our stay of Factory F both the different week-ends and a munition workers' holiday we collected as many samples as we could, first when the girls left for the week end or holiday, or immediately after they reached their destination, and again just before they returned on Monday (or at the end of the four days'

holiday. There was in the average a decided drop in the intensity of the reaction, some urines almost completely cleared, but many still showed a good deal of the T.N.T. derivative on the Monday morning. (See Appendix A for details.)

The two girls above-mentioned resumed wearing the respirators on Saturday, September 9th, their faces having healed with the rest, and they wore them constantly while at work until Friday, September 15th, thus making a complete week. They could not stand the respirators any longer, on account of the skin irritation and discomfort. The results of the urinary reactions were as follows :—

V. McC.

Saturday, September 9th ... ... R. 4
Wednesday, September 13th ; Thursday, September 14th ; and Friday, September 15th ... ... R. intense each time

L. F.

Saturday, September 9th ... ... R. 3
Wednesday, September 13th ; Thursday, September 14th ; and Friday, September 15th ... ... R. intense each time

It is thus seen that in the three later days of the week of wearing the respirator the reaction for T.N.T. in the urines of these two girls was "intense," and as no visible effect on the urine had been obtained and the respirators were making the girls' faces sore, the experiment was discontinued.

Experiment 2 in Shop No. 2. Four girls wore respirators, of whom two left the works in the course of the experiment. This was compensated for by the behaviour of one of the other two girls, E. S., who wore her respirator well and uncomplainingly for nearly a fortnight. This girl did all in her power to help us, being interested in the work, and she later helped us in the complementary experiment with her hands protected from contact (see below).

(1) L. G. Started wearing respirator Tuesday, September 5th, and wore it till September 8th. Urinary reactions : September 7th, R. intense ; September 8th, R. intense. Left works.

(2) S. T. Started wearing respirator Tuesday, September 5th, and wore it from Tuesday, September 5th, till Saturday, September 9th, then again the next week on Monday and Tuesday, when she also left works. Urinary reactions : Tuesday, September 5th, R. 3 ; Thursday, September 7th, R. intense ; Saturday, September 9th, R. intense.

(3) R. A. Wore respirator from Tuesday, September 5th, till Saturday, September 9th, and again in following week from Monday, September 11th, till Saturday, September 16th ; but it was more irksome to her than to next subject (E. S.), and she occasionally took it off. The greater part of the period, however, she wore it. Urinary reactions : Tuesday,

September 5th, R. 3. Saturday, September 9th, R. 4. Tuesday, September 12th, R. 3. No later specimens obtainable.

(4) E. S. Started wearing respirator on Tuesday, September 5th, wore it constantly and well and was keen on wearing it, up to and including Friday, September 8th. She did not come to work on Saturday, September 9th, but rested at home and did not go near any T.N.T. She resumed wearing it on Monday, September 11th, and wore it constantly while at work until Saturday, September 16th inclusive, that is, one day less than a fortnight of working periods. Urinary reactions: Tuesday, September 5th, R. 3. Thursday, September 7th, R. 2. Friday, September 8th, R. 4. Tuesday, September 12th, R. 4. No later sample obtainable. (Contrast these with results of skin protection in this same girl as given below.)

As there was no diminution in the reaction and the girl's face was being made sore by the respirator pad, the experiment was discontinued.

There is thus no evidence that in any of these girls there was any decrease in the amount of altered T.N.T. being excreted as the result of wearing the most complete respiratory protection that could be suggested.

(iii) *Experiments on Absorption by the Skin alone, other channels being purposely excluded.*

The above experiments having shown of how small importance absorption from the air by swallowing or breathing is in the ordinary workshop conditions, we determined to make a series of experiments upon ourselves in which only the hands or the feet should be exposed to the poison. For the purpose easily to do this when the subject of experiment carefully refrained from going near any part of the factory or workshops where there was any T.N.T. dust or fume. After showing by the application of the urinary test that our systems were free from T.N.T., we either rubbed T.N.T. into the palms of our hands (much as a girl would be exposed to T.N.T. contact in handling pellets) or else dipped it into our socks.

Experiments 1 and 2 made on B. M. After refraining from visiting the workshops for a day the urine was tested and showed only the faintest trace of T.N.T. reaction. While walking about in the large orchard attached to the factory, B. M. rubbed T.N.T. into the palms of his hands by rolling about in the hands an amatol pellet containing 20 per cent. T.N.T. After two hours a specimen of urine was passed, and this showed a distinct T.N.T. reaction. This reaction went on increasing until next day when there was quite a strong reaction, lying in intensity about as the average given by the urine of the shop worker. The rubbing in of the amatol on the previous day had been kept up intermittently for about six hours, after which the hands were washed with soap and water. The T.N.T. reaction remained in gradually

decreasing intensity for a period of ten days, after which the urine became clear, although B. M. neither rubbed T.N.T. in again, nor went near any source of dust or fume.

The first morning after rubbing in, B. M. awoke with all the symptoms of a minor attack of T.N.T. illness.

He had a marked frontal headache, a feeling of nausea, and intermittent abdominal pain. This abated towards evening, but a feeling of malaise and drowsiness persisted for about two days.

After a fortnight, and when his urine had become free of T.N.T. reaction, B. M. repeated the experiment with the same results as above.

Experiments 3 *and* 4 *on G. A. W. and T. A. W.* Dr. Wyon and Mr. Webster then dusted T.N.T. powder into their socks and worked during the day in the laboratory, but quite away (at least 100 yards) from all dust or fume. The result was that each obtained a distinct but slight trace in the urine, which previously to the experiment had been quite clear. The amount, however, was nothing approaching that in the case of B. M.

These two observers then rubbed T.N.T. into the hands with similar results, namely, a slight trace in the urine.

Urinary Reactions.—*T. A. W.:* September 15th, 1916, hands rubbed with amatol (20 per cent. T.N.T.) in lanolin; two hours later, R. a trace. September 19th, similar experiment; urine after three hours, R. a trace; next morning, nil. October 5th, both socks sprinkled with amatol at 9.30 a.m.; urine at 10.30 a.m., R. nil; at 12.45 p.m., R. nil; at 3 p.m., faint trace; at 6 p.m., trace; next morning at 11 a.m., trace. *G. A. W.:* September 25th, hands rubbed with T.N.T. in lanolin at 1 p.m., washed at 1.30 p.m., T.N.T. rubbed in again at 3.30 p.m., and rubber gloves worn; urine at 11 a.m. (control), nil; at 4.30 p.m., trace; next morning at 10 a.m., nil. October 5th, amatol sprinkled in left sock at 9.30 a.m.; urine at 10.20 a.m., nil; at 12.45 p.m., nil; at 5.30 p.m., faint trace.

This varying absorption by the skin is important from the light it casts on individual idiosyncracy. It becomes obvious that some individuals let the poison through the skin with ease, while others by the nature of their skin bar its entry, so that on the same job the system of one would be fully exposed to the poison, while the system of the other might be comparatively free.

Again, the long delay in the clearing up of the urinary reaction showed that the susceptible person whose skin had become loaded with the poison might continue under the influence of the drug for days after his apparent removal from it by absence from work, owing to the gradual unloading of the reservoir of T.N.T. in the layers of his epidermis.

This conclusion casts light on the increase of symptoms, even in cases that recover, often seen for some days after removal from outward contact with T.N.T.

The problem no longer rests upon the evidence of our own three cases above; it has since been established by tests applied to many people, such as laboratory workers never before exposed to T.N.T. inhalation, and to oncoming T.N.T. workers before any exposure.

The technique used for the detection of the T.N.T. derivative in the urine has been worked out on quantitative lines by G. A. W. with the view to supplying a preliminary test for the purpose of discovering those persons especially susceptible to absorption and keeping them away from T.N.T. work. These experiments were conducted after the Eyserheim period, and will be described later under the heading "prophylactic measures," but an outline of the results is presented here to round off this section on variable absorption from skin alone.

The later experiments showed that B. M. gives a distinct T.N.T. reaction in the urine when as little as 10 milligrams of T.N.T. in one per cent. solution in acetone is rubbed into the palm of one hand, while G. A. W. shows no reaction after rubbing 100 milligrams over hand and forearm. It is interesting that G. A. W. gets a dermatitis while B. M. gets none.

The fact that G. A. W. does not give the reaction from even 100 milligrams is not due to a holding up of T.N.T. by the liver and kidneys after its passage through the skin first because G. A. W. has no symptoms of T.N.T. poisoning, and, secondly, on the grounds of the result of a direct experiment. When G. A. W. injected hypodermically only 5 milligrams of T.N.T. in olive oil, he obtained at once not the reaction in his urine.

The conclusion is thus clearly established that B. M. possesses a permeable skin for T.N.T., and G. A. W. an impermeable skin. It is confirmed by a work-shop experiment with B. M. and G. A. W. as subjects, to be described later.

The next experiment was carried out on nine laboratory persons (including B. M. and G. A. W.), of these B. M. was the only one to give a positive result with 10 milligrams, but two laboratory boys L. L. B. and L. W. C. gave positive results with 20 milligrams. The T.N.T. in all these cases was applied to the palm in 1 per cent. solution in acetone.

A large scale experiment is now being made upon all oncoming workers at a certain munition works. In the course of this many men and women have already been tested; the results are here given to prove the truth of skin absorption and its high variability by the consideration of a large number of cases.

Men operatives having 10 milligrams in acetone applied to the palm showed in 33 cases only 3 per cent. of positive result, i.e., 32 were negative, 1 positive. When the dose on the palm was increased to 15 milligrams, out of 119 men tested 27 (23 per cent.) were positive and 92 (77 per cent.) negative. When women operatives were tested similarly with 7 milligrams, out of 107 cases 15 (14 per cent.) were positive and 92 (86 per cent.)

negative. On increasing the dose to 10 milligrams, out of 65 cases 19 (29 per cent.) were positive and 46 (71 per cent.) negative.

(iv) *Experiments on the Effects of Skin Protection in Diminishing Absorption.*

Experiment 1. The greatest difficulty was experienced in keeping the hands of factory operatives clear and free from contact with T.N.T., on account of holes in gloves, T.N.T. dust getting under gloves, and, in intervals of work, operatives removing gloves, or touching contaminated surfaces before putting on gloves. There was no disposition to thwart our work, we experienced great patience on the part of most employees, but the problem was like that of teaching the principles and practice of aseptic surgery to a lay person without technical knowledge, or any considerable education, in a week or two of time.

We only succeeded in keeping the hands chemically clean for over a week in one girl, E. S., who had previously helped us so well in the respirator experiment.

This we could only manage by asking her to come to our laboratory when going on or coming off from each working period, so that we could test her hands with alkaline alcohol to make certain T.N.T. had not penetrated to the skin, and by putting on and taking off the preventive coverings ourselves and thus making certain this was done without any contamination.

After several failures, we finally achieved our object by putting next the skin of the hands a pair of rubber gloves, then bandaging with an ordinary three-inch surgical bandage over the top of the rubber glove so that no powder could fall in between glove and hand. The bandage reached from wrist to elbow, and protected wrist and forearm. In order to preserve the rubber glove from mechanical injury, an ordinary pair of cotton gloves, such as are supplied in the workshops, was worn on top of the rubber gloves.

The girl was quite able to work in this outfit as no delicate finger manipulation is required in the process.

For nearly a fortnight, from October 10th till October 23rd, 1916, inclusive, we were able to keep her hands continually clean as shown by the alkaline alcohol test.

The reactions of the urine when she was wearing a respirator have been given above. In the period with no respirator or the shop respirator only, and with hands unprotected or partially protected in various ways, her urinary reaction had varied between 2's and 4's, that is about the shop average, as follows :—

Urinary reactions period previous to hand protection : September 22nd, 1916, R. 4 ; September 25th, R. 2 : September 27th, R. 4 ; October 2nd (*Monday before work*), R. faint trace ; October 5th (morning), R. 3, (night), R. 2 ; October 6th (Friday morning), R. 3 ; October 9th (Monday morning), R. trace.

It was on Tuesday, October 10th, 1916, that we first managed to get her hands free at the end of a shift, and this was maintained

until Tuesday October 24th, when they became fouled through a hole appearing in a rubber glove. The urinary figures for this interval with clean hands were as follows: Thursday, October 12th, R. trace; Friday, October 13th, R. 1; Saturday, October 14th, R. trace; Thursday, October 19th, R. trace; Friday, October 20th, R. 1; Saturday October 21st, R. 1; Monday, October 23rd, R. nil; Tuesday October 24th R. 2 (on October 24th hole in rubber gloves and hands contaminated).

This experiment clearly shows the value of hand protection. The traces in the urine are just about those which would be anticipated from the small amount of dust in the air. Such traces are obtained by purposely swallowing the amount of T.N.T. indicated by the dust extraction experiment (see below) as being the amount inspired by a worker during a shift.

Experiment 2. The difficulty encountered in keeping the hands of operatives chemically clean from T.N.T. and being certain that the whole experiment remained under our control induced us to institute an experiment in which we should work ourselves in the workshop upon the same task. Accordingly, the writer (B. M.) and a voluntary co-worker, Miss M. G. Francis (M. G. F.) worked for a week on one of the same machines operated by the factory employees and under similar conditions in the same shop.

All protection to mouth and nose was dispensed with, but the hands were thoroughly protected by leather gloves next the skin and rubber gloves outside of these. At the termination of each working period, a negative result was obtained on testing the skin of the hands with alkaline alcohol, so proving that we had attained to complete hand protection.

There was a high wind on two of the days of the experiment, which blew some of the T.N.T. powder into the air, causing even the workshop employees to complain to one another of the discomfort of the powder in the air. The two experimenters, like most beginners, felt it severely and suffered from sneezing and running from nose and eyes, requiring the copious use of "respirator refills" diverted from their usual purpose to act as substitutes for pocket handkerchiefs. Yet neither of them with hands so protected showed more than a small amount of the urinary reaction at the end of a shift, and this only for a few hours thereafter, and each day they were usually clear of it before the resumption of work. (See Appendix C.)

The usual employees of the factory working alongside had on the average at least five times the quantity in the urine, although wearing respirators according to regulations at that date, but their hands were heavily laden with T.N.T., while those of the two experimental workers were free from it.

It had been intended to carry out the converse of this experiment in the following week, when it was designed that the two workers should operate in respirators, but with the hands unprotected.

Unfortunately a fire, followed by an explosion, wrecked the workshop in which the experiment was to have been performed, and the experimenters only escaped being involved by a detention in London on business connected with T.N.T. poisoning.

This portion of the experiment was subsequently carried out by B. M. and G. A. W. at an exploder bag filling factory B., and as it is the proper corollary to the above experiment it may be placed here.

Experiment 3 at *an exploder bag factory B.* On June 4th, 1917, the two experimenters, G. A. W. and B. M., spent a whole period of working in the factory, close to the actual workers, so that they would take in (by breathing and swallowing) the same amount of dust and fume in the air as the workers take in by these channels. They did no work on machines during this period, and protected themselves from all contact, save that of inhalation by mouth and nose, but in this latter respect they were as much exposed as any operatives.

On the following day the precautions against skin absorption were set aside, and the two experimenters proceeded, with bare hands, to manipulate the machines and behaved like ordinary workers.

The results given below show the contrast, in these two days of a workshop experiment, between a worker exposed to all inhalation of dust and fumes and a worker exposed in addition to actual skin contact with the deleterious substance. They show also the difference in degree of absorptive power of two different workers.

——	June 4th. Idling in workshop with hands protected.	June 5th. Working machines with hands exposed.
Urinary reaction at end of shift.	G. A. W., very faint trace. B. M., faint trace.	G. A. W., R. 1. B. M., R. 3.

This experiment accordingly confirms the results of the rubbing-in experiment and of experimental exposure to the acetone solution of T.N.T. (see above).

(v) *Determination of the Actual Amount of T.N.T. in the Air of the Workshop and Estimation of the Maximum Amount which could be Breathed by a Worker during a Shift.*

A prolonged experiment of this kind had already been made elsewhere, but without any attempt at exact quantitative accuracy. No elaborate apparatus was at our disposal, so we utilised as interceptors two large U-shaped calcium chloride drying tubes fitted with rubber connections in series. Electric connections were taken to a vacuum pump, which was placed in the open air to avoid all danger from sparking. The mouth of

the absorbing U tube was placed in as nearly a similar position as regards T N T dust as the worker's mouth and nose as could be arranged. The gas circuit passed in series through the two U tubes, then to a gas meter showing litres, and hence to the vacuum pump. The pump was run approximately at intervals of twenty minutes on and ten minutes off to avoid heating of bearings, and this was continued for a whole shift period. The U tube as well contained water which was renewed at intervals as it evaporated to catch the T N T dust. The second U tube was empty and used as a trap to determine whether all the T N T dust had been stopped. On testing with alkaline alcohol at the end of the experiment the tube gave no pink colour, thus showing that all T N T had been absorbed by the first U tube.

The water in the first tube showed floating in it a number of particles of insoluble powder, but the amount was seen to be small. The contents were taken down to dryness on a bath and extracted with ether in which T N T is very soluble. The ether was poured off into a weighed glass vessel and evaporated off and the vessel and contents weighed. The increase in weight showed the amount of T N T obtained from the number of litres registered by the meter, a mean of three experiments gave 11 milligrams, equivalent to 0·18 gram, or a pan's head quantity. Details of the experiments and calculations are given in Appendix B.

(vi) *Effect on Authors of Swallowing Known Amounts of Pure T N T.*

Now that we knew by direct analyses the amount of T N T in the factory air and also the degree of reaction of the urine when working in the factory but with hands protected, it became interesting to test whether swallowing the small amount of T N T directly indicated by the air analyses would give to the urine the same degree of reaction as if it had been breathed in while working.

The air analyses had been obtained before M. G. F. and B. M. started their week's experiment in the shop with their hands protected as described above. While they worked in the shop G. A. W. and T. A. W., refraining otherwise from going anywhere near sources of T N T absorption, administered at the usual hour doses of T N T to G. A. W. taking 15 milligrams daily while T. A. W. took to refrigerate daily amounts lying at about the level which the air analyses showed might be taken up from factory air.

The urinary reactions obtained ran at the same levels as those obtained by B. M. and M. G. F. in the shop, using as Test 1 and "during" controls. Details are given in Appendix C for comparison with workshop results with protected hands. A comparison of these three sets of results shows, therefore, a close correspondence between the amounts in the air, the amount swallowed and inhaled, and the resultant urine reaction.

Moreover, it is clearly shown that this is only a small fraction of the amount taken up by the average shop worker, and there is complete nightly clearance.

The above experiments taken in their entirety appear to us to afford concordant evidence not only that T.N.T. is absorbed by the skin, but that under ordinary average workshop conditions this is by far the most important channel.

Observations were made at Factory F. indicating the close connection between minor T.N.T. illness and toxic jaundice or aplastic anæmia. In order to avoid splitting up the clinical evidence this portion will be reserved till after the next section dealing with a research at a National Shell Filling Factory.

III. Researches at a National Shell Filling Factory (*A*).

These inquiries were carried out in November, 1916, and the particular factory selected was chosen because it was one of two national factories which showed *at that period* the highest incidence, both in minor T.N.T. illness and in notified cases of toxic jaundice and deaths from toxic jaundice.

It has since turned into one of the healthiest in the country, and a member of its medical staff recently informed the writer that he attributed this happy result to the early detection of cases by a medical officer patrolling the workshop. The other two changes which have been made, as we have been informed by several visitors to this factory, are that all the processes are carried out with greater cleanliness, and, secondly, that increased forced ventilation has been introduced.

The analysis of the air of one of the chief workshops of this factory where most of the cases of toxic jaundice and fatalities had occurred shows how very little T.N.T. dust or fume was present (see Appendix B), so that, in our opinion, this cannot be an important factor in the change for the better.

The results obtained here formed confirmations and extensions of our earlier work; they have already been given in another report and so need only be epitomised here.

(1) It was shown that because enough stress had not been laid on the danger of skin absorption sufficient attention was not being paid to keeping all processes clean. As a result, persons engaged in cleaning up the soiled shells with oily rags were often cyanosed, and amongst such persons then classified in this factory as "shell finishers" there had been several cases of toxic jaundice.

(2) That the chipping off and rubbing with oil did not completely remove T.N.T. from the outside of the shells, so that these went on to the so-called "clean shell store" covered by a film of oily T.N.T. This accounted for the presence of T.N.T. cyanosis and illness in the "clean shell store," and for the occurrence of cases of dermatitis here. This and the fact that railway men loading filled shells on to railway trucks had been cyanosed or jaundiced showed again the importance of skin absorption.

(3) Statistics were obtained of the various sections which showed clearly the great importance of minor T.N.T. illness in causing sickness and absenteeism. The measures since taken have greatly reduced this loss.

(4) Comparative statistics were also collected, showing that those employees who worked close to molten T.N.T. and fume possessed as good a record as to health and attendance for average periods engaged on the job as did other workers much more remote from the molten T.N.T.

(5) Similar experiments to those conducted at Factory F showed that the factory air close to the cylinders of molten T.N.T. was even better than at Factories F., and that we only obtained a minute trace in our own urines after remaining for an entire shift close by the position at which the molten amatol was poured.

This was confirmed by our analysis of the air during the same shift, our estimations yielding only 6 milligrams, or less than one tenth of a grain, as the available amount per worker per shift.

The greater part even of this small amount of absorption was caused at two short intervals during the shift, when the workmen, engaged in cleaning up, chipped off from the floor a layer of congealed amatol at least half an inch thick all round the pouring places, scraped it away with metal scrapers, and swept it up dry.

Our analyses also demonstrated that there were practically no nitrous fumes in the air. (See Appendix B.)

(6) Analyses of the records of fatal and non-fatal cases were given, showing what a large proportion were truckers and finishers (cleaners) who were largely exposed to skin contact and comparatively much less to dust or fume inhalation.

IV. Action of T.N.T. in the System, and the Connection of Minor T.N.T. Illness, Toxic Jaundice and Aplastic Anæmia.

(1) *Action of T.N.T. on the Blood.*

Tri-nitro-toluene belongs to a very large class of bodies, including both the organic nitro-compounds and their reduction products the amino-compounds, which possess the common character, that of acting in the first instance on the blood. This action is based on a change in the hæmoglobin, which is to a varying degree converted into a mixture of NO hæmoglobin and met-hæmoglobin. Since these hæmoglobin derivatives cannot function as oxygen carriers, it follows that, when more than a certain fraction of hæmoglobin has been altered by the action of the poison, oxygen dearth appears, more conspicuously so when any exertion is attempted. This is the stage of minor T.N.T. illness, varying in degree from case to case according to the degree of deficiency of active hæmoglobin.

The symptoms complained of by the patients are very similar to those of mountain sickness, such as breathlessness, tightening in throat and chest and difficulty in breathing, giddiness, drowsiness, nausea, abdominal pains, general malaise, appetite at first stimulated, then lost.

The changes in *appearance* observed before any jaundice occurs are also due to the changes in the blood. A drop of blood obtained by pricking shows a venous blue colour which does not soon turn scarlet when exposed to the air or when absorbed by blotting paper; this effect is quite characteristic and might be used for diagnostic purposes.

This alteration in the colour of the blood shows itself by producing ashen-blue lips, and also in many cases by giving a peculiar pallor to the face which simulates anæmia but is not anæmia, for counts of red blood cells and estimations of hæmoglobin give normal figures in these cases of minor T.N.T. illness.

Although there is a normal number of red blood cells and a normal hæmoglobin index there is considerably increased labour thrown upon the hæmatopöietic organs due to the increased rate of breaking up of the altered red blood cells and the increased rate of production of hæmatocytes, balancing this loss, with an overworking of the red marrow hæmatoblasts. Similar effects occur in malaria and in various forms of jaundice.

Evidence of such destruction and regeneration is afforded by the very frequent statement volunteered by these patients that their urine turns dark-coloured during an attack, and by the frequent presence of bile-stained serum.

The relative degree and incidence of this cyanosis and its attendant symptoms differs with the different organic nitro-compounds and also in the case of the same nitro-compound according to the species of animal to which it is administered. So also does the frequency with which these minor symptoms lead on into toxic jaundice differ in different animals and with different drugs of this class.

These facts are in interesting keeping with the results obtained industrially upon human beings with other nitro-compounds than T.N.T. *which are more directly poisonous when absorbed*, such as dinitrobenzene and dinitrophenol. These drugs would appear in man to cause death before the toxic jaundice and the typical liver lesions have had time to develop, as does T.N.T. itself in the case of the cat, to which animal it is more toxic. A case of toxic jaundice was, however, reported some years ago due to dinitrobenzene, and it is here to be remembered that T.N.T. before its present enormous production had the most innocent reputation of any of the group.

It may be added that when given in large doses T.N.T. also kills without any jaundice or liver lesions in all the types of animals subjected to experiment, viz., white rats, guinea pigs, rabbits and cats.

The lesions in liver and bone marrow accordingly seem to appear in those species of animals not specially susceptible to the poisoning, as a later and more or less chronic effect, preceded by other changes.

(ii) *Toxic Effects of T.N.T. compared with those of Dinitrophenol.*

The effects of dinitrophenol, which has recently been manufactured and manipulated on a large scale abroad, are remarkably similar to those of tri-nitro-toluene, and furnish an interesting example of what has just been stated above.

Over a year ago we investigated the toxicity of dinitrophenol amongst a number of other nitro-compounds at the request of the Department of Explosives Supply, and reported that it was much more poisonous to laboratory animals than tri-nitro-toluene or any of the other substances submitted.

This opinion is substantiated by a report on "Intoxication by Dinitrophenol," by Professor Etienne Martin, Medecin Major de 1re classe, and his colleagues in France.* This substance appears to be much more dangerous to the workers than T.N.T., a considerable number have died from its effects, and even as with T.N.T. a much larger number have suffered minor poisoning and been incapacitated from work.

The symptoms of the more serious cases, as described by the French observers, are strikingly like those of T.N.T. as described by ourselves and others.

"The most serious cases are characterised at first by pallor with slight cyanosis of the lips, a virile dyspnœa with a feeling of tightness in the chest."

"The most frequent attacks have been gastro-intestinal, take rapid course, a fetid anorexia, vomiting and a moderate slight jaundice, and a little albumen in the urine."

"Transient headache and vertigo are complained of by many workers."

"The workers show marked 'cachexie.' They have a feeling of constriction nipping them at the base of the chest which interferes with respiration."

All these are the same symptoms as are shown by observation of workers on T.N.T. in this country, and the basis is the same, namely, an action on the hæmoglobin of the blood, but the dinitrophenol is more poisonous and kills before liver lesions have had time to appear.

The French observers state that these facts rather point to absorption of the poison through the pulmonary and digestive tracts, but they do not appear to have made any determinations of the amount of dinitrophenol dust in the factory air, and it is significant that 17 out of 27 deaths occurred amongst workers engaged in weighing, cleaning and melting the product, who would be exposed heavily to skin absorption.

They make the statement, however, that "Lastly, in the case of all the workers one must not lose sight of the great cleanli-

* Our thanks are due to Dr. F. M. Legge, Home Office, for the information used.

of absorption of dinitrophenol by the skin of the hands and forearms."

It would appear from this, and especially if dinitrophenol is to be introduced upon any large scale in this country, that quantitative experiments ought to be instituted as to the amount of dinitrophenol in the air under ordinary workshop conditions and the amount taken up by the skin.*

Laboratory experiments are now being made by us upon animals and ourselves as to the channels of absorption, and if these show us that skin absorption occurs the problems of prophylaxis would be identical with those already used for T.N.T. (See Appendix E.)

It is interesting to note, in view of what we have found in the case of tri-nitro-toluene, that dinitrophenol is also reduced in passage through the body to a mixture of mono- and diamino-phenols, which give distinctive colour reactions. The reduction appears to occur in the liver. There are no microscopic lesions in any of the organs, possibly for the cause assigned above.

(iii) *Minor T.N.T. Illness caused by Blood Change.*

Returning to the consideration of the minor T.N.T. illness caused by the initial blood change it may be pointed out that, although this is termed "minor," it is probably of "major" importance from the point of view of national economics.

In the earlier period of our researches there were at several filling factories hundreds of workers "off work" and on compensation pay owing to "minor" T.N.T. illnesses. All over the country there must at this period have been some thousands of workers temporarily incapacitated, and the economic loss in labour and money must have been very large. In addition this large tide of minor illness was giving the T.N.T. occupations a bad name and cutting short the supplies of labour.

Now as a result of cleanliness of labour and of early detection of susceptibles and sending them off to other work, this evil has been combated, and the number of workers "off work" from minor T.N.T. illness has largely abated.

* A remarkably interesting observation of the French researchers appears to show that dinitrophenol both goes in and comes out by the skin. "When a worker is going to be affected by dinitrophenol the parts of the skin protected by the clothing, such as are not likely to be stained by dinitrophenol (the chest, shoulders, back and upper arm) assume a patchy yellow colour. It appears to be an excretion of sweat containing dinitrophenol. On the other hand, workers who are unsusceptible show the staining only in the uncovered parts, such as the head and hands. This symptom is of importance, as it shows that the sweating comes on when the organism is impregnated with dinitrophenol; it is an indication for suspension and treatment." Many T.N.T. workers have assured us that they sweat pink sweat under the armpits, where there would be little chance of direct contact with T.N.T. dust.

(iv) *Action of Pure T.N.T. and of Impurities.*

It has been often discussed amongst those interested whether minor T.N.T. illness is due to absorption of tri-nitro-toluene itself or to nitrous or other fumes which come off the crude T.N.T. or to impurities such as the di-nitro-toluenes or the nitro-naphthalene compounds present in small amounts. Some have suggested that tri-nitro-toluene causes the cyanosis and the minor T.N.T. illness, but that toxic jaundice may be caused by something else, such as a liquid impurity or fume, and possibly aplastic anæmia by some other unknown substance.

It is exceedingly difficult to provide a rigorous proof that the whole of these effects are due to tri-nitro-toluene and to tri-nitro-toluene only and are all causally related, but we may say that (1) as the result of direct experiments with pure tri-nitro-toluene, (2) of exclusive experiments with all the various impurities we could obtain, (3) of negative results in attempts to obtain fumes or volatile impurities in the workshop, and (4) of several personal observations of transitions from minor T.N.T. illness into toxic jaundice, we are strongly of opinion that all these effects are caused by the same substance, tri-nitro-toluene, and that they are probably closely connected in their mode of causation.

Administration of *pure* T.N.T. to kittens either by mouth or injection rapidly produces cyanosis, dyspnœa, and often nausea and sickness; the animals are then obviously suffering from minor T.N.T. poisoning. A larger dose kills them from acute T.N.T. cyanosis. Rodents show it less markedly, but a degree of cyanosis is produced here also.

One of ourselves (T. A. W.), taking by mouth 50 milligrams of *pure* T.N.T. daily and not going near any other exposure to T.N.T. for a period of ten days, became distinctly cyanosed, and his blood was shown spectroscopically to contain met-hæmoglobin.

Workers filling "exploder bags" with *pure* T.N.T. and not anywhere in the vicinity of other T.N.T., have become markedly cyanosed, and some have acquired toxic jaundice and died on such occupations. (See records of cases below.)

There is no evidence that workers with crude T.N.T. containing a large percentage of impurities have been any more severely hit than workers with the purer qualities, nor that those working near molten crude T.N.T. where there would be much more volatile impurities, have been more severely attacked than those working remote from such sources of volatile impurity.

If an impurity present only to the extent of a fraction of one per cent. in a factory sample of T.N.T. is to be regarded as a causative agent of any importance, it must evidently when isolated and administered by itself have a proportionately more lethal effect. For example, if it be present to the extent of one per cent., then in neat condition after isolation it should be approximately one hundredfold as poisonous as T.N.T. and also produce the observed effects of T.N.T. illness.

No such substance is known. We have, through the kindness of Messrs. J. Leitch & Co., been supplied with samples of all three of the isomeric di-nitro-toluenes in pure condition which are only present in small amount in crude T.N.T. We have tested these on animals and only found them of the same order of toxicity as the tri-nitro-toluene. So far as there was any difference they were somewhat less toxic.

Again, samples of the various impurities separated from crude T.N.T. in the processes of purification necessary to obtain a purer product for filling "exploder bags" and for other purposes were placed at our disposal by a large manufacturing firm. These were examined and tested, and none of them showed any substance possessing a higher degree of toxicity than tri-nitro-toluene itself.

It has recently been shown that in certain processes of nitration the methyl-group in the toluene molecule ($C_6H_5.CH_3$) is split off to a certain *minute* extent, and as a result the crude nitration product contains a certain amount of benzene-nitro-compounds and nitromethane compounds. These latter compounds resemble chloroform and carbon-tetrachloride in their chemical structure, except that instead of chlorine the nitro-group (NO_2) takes a place in the molecule. They are well known to be very poisonous. One of them, tetranitromethane, has recently been isolated and investigated by Mr. F. W. Linch, chemist of Explosives Supply. But this substance is only present when certain processes are used, and is then only found in the crude product to the extent of 0·12 per cent.* Moreover, the toxic effects produced by it are quite different from those of T.N.T. poisoning.

On all the above evidence, it becomes clear that tri-nitro-toluene itself, and not any volatile impurity or fume, is the cause of the blood change and of the cyanosis, pallor, and clinical symptoms so produced, known collectively as "minor T.N.T. illness." The evidence that the toxic jaundice and liver lesions are also caused by *pure* tri-nitro-toluene is scarcely less clear.

(v) *Causes of Toxic Jaundice and Aplastic Anæmia.*

1. *Preliminary Discussion.*—In the laboratory experiments, as will be recorded later, we have obtained in three rabbits liver lesions which on microscopic examination showed necroses and fatty degeneration closely resembling the early stages showing in the liver lesions in human beings dead from T.N.T. poisoning. Also in one of these animals there was distinct jaundice, all the tissues and serous fluids being bile-stained.

In the workshops several fatalities have occurred amongst workers who had never been near crude or molten T.N.T. and worked only with the purest industrial form of re-crystallised

* The greater part even of this small amount would be removed before the T.N.T. reached the shell-filling factories.

T.N.T., which would only contain a fraction of one per cent. of impurity. We have ourselves seen jaundice following on cyanosis where only pure tri nitro toluene was used.

As regards aplastic anæmia the number of cases is small, but there is one case (S. S.) where employment on pure T.N.T. only in filling "exploder bags" caused toxic jaundice in December, 1916; this was recovered from in February, 1917, but *without any new contact with T.N.T.*, aplastic anæmia developed in March and April, 1917. This suggests the intimate connection of toxic jaundice and aplastic anæmia, and also the common root of both in exposure to tri nitro toluene. Other cases of death from aplastic anæmia have shown at the autopsies similar lesions to the liver to those characteristic of toxic jaundice.

The ground becomes less certain when the question is considered, whether the initial blood changes predispose to toxic jaundice and aplastic anæmia, and in a certain number of cases lead on into these more grave affections.

No rigorous proof can be given, and the decision, as in many legal and clinical cases, must be made on the weight and look of the evidence. It must be remembered that the majority of our beliefs in medicine are reached by such a process, and not by deductions possessing mathematical exactitude.

The best plan will be to put evidence before the reader and discuss the underlying physiology of the conditions induced by the primary poisoning in the blood, and then leave the judgment with him.

The great practical importance of the issue is whether persons distinctly cyanosed or showing in other ways signs of minor T.N.T. illness should be turned off T.N.T. work.

If there were no connection between cyanosis and toxic jaundice, these persons might safely be left on, and many strongly cyanosed individuals have been left on without toxic jaundice developing for many months. This by no means proves the matter as we shall see presently and in the opinion of the writer many lives were lost earlier in the campaign by the cyanosis not being used as a danger signal.

The picture given by us in 1916 for diagnosis and prognosis relies practically entirely on cyanosis, the stage of jaundiced conjunctivæ is too late. We believe that the enormous reduction of incidence of all T.N.T. illness is largely due to the use of this sign. The conjunctivæ must certainly be watched, but so also must the lips and face, and the more attention is paid to lips and face the smaller number of cases there will be of jaundiced conjunctivæ to report.

This, however, it must frankly be admitted, does not show that toxic jaundice follows on as a resultant of the blood changes, and not as a direct poisonous effect upon the hepatic parenchyma. What it does show is that the cyanosed person is not one of those with a good skin protection, but is one who has let in the poison

which may now attack both blood cells, liver cells, and bone-marrow cells, either simultaneously and directly, or seriatim and indirectly.

The important matter from the preventive point of view is that cyanosis and its accompanying pallor form the best danger signal we possess, that liver and bone marrow are in the firing zone, and so long as there is in the country a sufficient supply of insusceptible people susceptible individuals ought to be removed.

To await jaundice as the danger signal is accordingly the unsafe course, to utilise definite cyanosis the safe one, and this apart from whether jaundice be due to direct attack on the liver, or indirect through oxygen-dearth, or a mixture of both.

2. *Physiology of Increased Hæmoglobin Metabolism.*—The first evidence to be taken is that for the existence of increased blood destruction as a sequence to formation of met-hæmoglobin. The importance of this investigation lies in the long-continued overwork which is presumably thrown upon the organs involved in the katabolism of the met-hæmoglobin and the regeneration of the new erythrocytes. These organs are the liver and the red bone marrow, and these are precisely the organs hit in the two graver issues of toxic jaundice and aplastic anæmia respectively.

The evidence for increased hæmoglobin metabolism will first be considered, and then that which has appeared to certain observers to negative it.

Increased hæmoglobin metabolism need not, and in other well-known pathological conditions often does not, lead either to jaundice, or increased deposits of iron in the liver, or the appearance of nucleated erythrocytes or poikilocytes in the blood, or to diminution in number of red cells, or reduced hæmoglobin content. All ordinary moderate cases of chronic malaria are examples of this fact. On the other hand, it is not denied that other agencies may produce any of the blood changes above enumerated.

The whole question centres around a labile physico-chemical reaction going on in the blood and the hæmatopoietic organs, and the point at which this reaction comes into balance like a reversible chemical reaction between hæmoglobin destruction and hæmoglobin regeneration.

The metabolism may vary within wide limits, as do many other metabolic equilibria in the system, without materially disturbing the equilibrium point, as shown by use of hæmocytometer and hæmoglobinometer.

The only set of substances which must be increased in their production as a result of increased hæmoglobin destruction are the waste pigments of the body, namely, the biliary and urinary pigments. If this increase be observed, it is clear evidence of greater hæmoglobin destruction because they arise only from such destruction, and they are that fraction of katabolised hæmoglobin which is not utilised in the red bone marrow for the anabolism back to hæmoglobin. The iron-containing fraction

is retained and utilised, and accordingly if anabolism is proceeding as fast as katabolism there need not be any accumulation of iron compounds in liver or elsewhere.

3. *Toxic Jaundice and Aplastic Anæmia as a result of Increased Hæmoglobin Metabolism.*—The results of the increased production of pigments will depend on the condition and activity of the organs which dispose of them, namely, liver and kidney. If, say, four times the normal amount of hæmoglobin is katabolised by the liver cells, and four times the normal amount of bile pigments so formed, and if now the liver cells excrete out into the bile canaliculi four times the normal amount of pigment, then there will be no accumulation of bile pigments in liver or plasma, or tissues. The liver parenchyma will, so far as this task is concerned, have to work at fourfold its normal rate, both in the chemical breakdown of the hæmoglobin and its after excretion into the bile stream. So long as the liver can cope with this all goes well so far as jaundice is concerned, and the only effect noticed will be increased biliary pigments in the fæces and probably a darkening in the urine due to an increased formation of urochrome. As regards the iron containing fraction, this may either be stored in the liver, or sent out at fourfold the rate, to the red bone marrow to supply the increased demand of the hæmatoblasts for iron compounds. If the iron is held up, there will be an iron starvation of the hæmatoblasts leading to some form of anæmia, but not to jaundice. This may appear both in diminished erythrocyte production and in appearance of undersized and irregular forms. On the other hand, if the liver discharges the increase of iron compounds into the blood stream, and this is fully utilised by the hæmatoblastic tissues, then the red marrow will now also have to work at fourfold the normal rate and may succeed in doing this or break down. If it breaks down, then there will be aplastic anæmia simply from atrophy and exhaustion, with an enormous drop in erythrocytes and a replacement of red by yellow marrow, but no jaundice will appear if the liver be functioning properly. There may also obviously be partial breakdown of both liver and red marrow functions when there may be both anæmia and jaundice present, or one may succeed the other as has been observed.

Let us consider a little more minutely the possibility that the liver is not able to excrete into the bile-stream the increased bile pigments as fast as it can form them by katabolising hæmoglobin. The effects will then vary according to what part of the hepatic mechanism has broken down. If the breakdown is in the hepatic parenchyma, this will become blocked with pigment, and probably commence to degenerate and atrophy, after a stimulation to a pathological regeneration, and at this stage there may be very little general jaundice. If the breakdown is in the bile canaliculi, their increased load causing obstruction or catarrh, then the bile pigments will be dammed back after production outside the hepatic cells, and they will commence to filter through into the

blood capillaries. The serum will now be loaded to a higher level with bile pigment, and this will stimulate the renal epithelium to take on the function normally performed through the biliary mechanism and excrete bile-pigments in the urine. The physical signs seen will depend on how far this compensation can be carried out, if it is incomplete, the concentration of bile pigment will increase until plasma and all serous fluids become bile-stained, and then jaundice is established.

In the great majority of T.N.T. workers, all of whom must be cyanosed in varying degree according to the extent to which they are absorbing, the compensatory balance is established, there is no critical breakdown in liver or red marrow or kidney, and the degree of minor T.N.T. illness varies with the degree of the blood change.

But any individual who absorbs freely is always in danger, some intercurrent illness or indiscretion may just tip over the balance and establish a condition which will run downhill of itself when once set going. Such persons ought obviously to be removed, so that a salting out process is established and the workshops become filled with those individuals who do not let in the poison.

It is, of course, possible that there may all the time be a direct attack of the poison on hepatic cells, hæmatoblasts, and renal epithelium, but the blood condition, if it exists, would form a powerful adjuvant to such a direct action and make all the difference between survival and degeneration of such tissues. In addition to the chronic overwork and organic fatigue, there is also to be thought of the continual pathological stimulus of heightened amounts of metabolites in solution in the cells, and the fact that when the rate of working is at a maximum these may be qualitatively different from normal metabolites.

4. *Indication of Increased Hæmoglobin Metabolism among T.N.T. Workers.*—There are two important indications of this heightened hæmoglobin metabolism found amongst T.N.T. workers.

In the first place, it is a common complaint amongst them, when suffering from minor illness, that their "water" became very dark-coloured during the attack. No bile pigments are present, but the colour shows an increase in the amount of urochrome.

In the second place, it has been noticed, in the first instance by Dr. Castellain, who has endeavoured to found an early diagnostic test upon it, that the serum of T.N.T. workers complaining of minor T.N.T. illness is often bile-stained before any colour can be seen on the sclerotics.

This cholæmia has been investigated by Dr. P. N. Panton* in the case of 100 women workers in T.N.T. not complaining of illness. This observer states that :—

* A report on the blood conditions of workers in tri-nitro-toluene by Dr. P. N. Panton, Clinical Pathologist, London Hospital.—*Lancet*, July 21st, 1917.

In twenty of the cases the serum was lipæmic. This would appear to show that in a high proportion of cases at least some action of the poison upon the liver was taking place. Alternatively, however, it may be that the fact that anæmia certainly increases the concentration of a small percentage of bile stained urea are found particularly among those subject to intoxication. All of these characters were present, but even in a percentage of twenty, this statistical area would seem unduly high. Nausea was noticed to be practically absent, and only three cases were at all deeply bile stained. Even a percentage of three cases of toxic cholæmia would lend support to the supposition that T.N.T. workers may be receiving damage to the liver without marked or unknown toxic symptoms.

It may be pointed out that since the sole source of bile pigment is katabolised hæmoglobin, whist this bile-stained serum most probably indicates is that the increased katabolism of the hæmoglobin reaches such a level that the liver cells and bile canaliculi are not able to pass it all through into the bile channels without some leakage into the blood capillaries due to its increased concentration in cells and tissue spaces.

It is hence difficult to agree with Dr. Panton in another section of his paper, where he states that

> The fatty absorption of T.N.T. does not materially have any deleterious effect on the blood.

> No degree of anæmia appears to have been present among the fifty workers examined. On the contrary, the red cells and hæmoglobin were well up to the normal standard.

As has been set out above, increased destruction of red blood corpuscles can occur without leading to any anæmia, provided the red bone marrow responds to the call and produces an equivalent number of new red blood corpuscles.

According to Dr. Panton's own observations there were in a certain factory 18 per cent. of the workers markedly cyanosed, and we are unable to conceive how this pathological condition could persist for months without any increased destruction of red blood corpuscles. In the majority of cases, in our opinion, a balance is established with increased destruction and increased production; in the small minority of cases such compensation fails, and this leads to toxic jaundice or aplastic anæmia.

3. *Possibility of the Direct Action of T.N.T. upon the Liver and Red Marrow.*—Beyond this point it is impossible at present to advance experimentally for us to exclude any direct action of the poison on the two main tissues concerned. We have no desire to maintain that such a direct action is impossible, but would point out that the two sites involved are those concerned in repairing a blood destruction.

A definite issue could only be obtained if there were some means of exposing liver and red marrow to attack by intravenous toluene without involving blood changes, and this is obviously impossible, because the poison must reach these tissues through the blood stream and will act upon the erythrocytes on the way.

The last remaining measure for a clear proof of direct action on these tissues without blood changes is a negative one, namely,

the supposed clinical observation that jaundice has been the first sign of attack without any precedent minor T.N.T. illness or evidence of cyanosis.

This position is surrounded by all the difficulties of a negative proof. It could only be admitted where there had been most careful examination of selected cases beforehand and thorough exclusion of other symptoms. Such proof has never been given, and the circumstances are not such that it can be given. Each factory doctor has a thousand or more of T.N.T. workers to look after, and it is quite impossible that he should examine each one of these daily and rigorously, and by scientific evidence, exclude blood changes. A great many of those cases where jaundice appeared to be the first trouble were antecedent to the introduction of workshop inspection or in places where there has been delay in introducing it. One occurred recently in which it was declared by doctor and welfare supervisor that jaundice was the first sign to appear and that there had been no cyanosis, but the case did not bear investigation, for intimates of the deceased at her home, lodging-house, and the workshop, volunteered the information that her lips had gone blue, and that she had suffered from breathlessness, giddiness, and sleeplessness. (See case records below.)

It is indeed difficult for a physiologist to conceive how there could be such a concentration of tri-nitro-toluene in blood plasma as to attack the liver parenchyma, cause degeneration of the liver to half its normal weight, and produce jaundice, without touching the blood cells, for which this poison like others of its class is known to possess such a strong specific affinity.

It may, we think, be assumed that tri-nitro-toluene in all cases attacks the blood, that this attack shows itself by indubitable physico-clinical signs, and that care over such cases and their early detection in the workshop is the surest safeguard against toxic jaundice and aplastic anæmia.

This position is supported by a large number of the returns in the monthly records issued by the Home Office, in which it is recorded that patients in earlier days were seen to be jaundiced by their workmates or by their intimate friends at home when they themselves did not know they were ill. The sequence of toxic jaundice upon minor illness and cyanosis is also shown by our clinical observations in the cases quoted below. It was these observations which led the writer in October, 1916, to make the following suggestions, which are quoted verbatim from a report then sent in to the T.N.T. Advisory Committee :—

24th October, 1916.

"Living, as I have done, amongst these workers for several weeks and going round the shops and examining daily, I have found that it is perfectly easy to detect the early cases of T.N.T. illness short of jaundice. There is a T.N.T. facies that is unmistakable, a pale face lacking in expression and like anæmia, but peculiar in itself, lips that can scarcely be described as cyanosed, but of an ashen-blue colour, similar gums, and

perhaps a faint trace of yellow on the conjunctivæ, the rest of the skin showing no icterus. In such a case questioning will often elicit a history of headaches, or nausea, or abdominal pains.

"The two fundamental recommendations arising out of these observations, are in the first place, the removal as rapidly as it can be accomplished of the susceptible individuals from T.N.T. work, and their replacement by fresh workers sent by the Labour Exchanges by priority to T.N.T. work. I estimate that there are between 5 and 10 per cent. of people at work on T.N.T. who should be sent to other work.

"The picking out is not a difficult task; it scarcely even requires medical skill; there is a foreman and a foreswoman who are right nearly every time they send them to me.

"It can only be done well by people who have some experience of them, and cannot be done efficiently by a visiting surgeon calling once a fortnight or once a week. The excitement of going to see the doctor—over which at present a great deal of munition time is wasted—tires up the patient and disguises the symptoms. The best way is to make a round the workshops and pick them out as they work or get the foreman or welfare superintendent quietly to draw attention to those suspected.

"The first weed out must be a large one, and it required both a rather crap of serious cases is to be avoided. The succeeding weedings will be small, and attention must be exercised on new beginners. Many workers have been engaged for over a year and never had a day of T.N.T. sickness, and these are often not very well developed physically or in any way resistant looking."

It is almost universally admitted, even by those who contend that there is no proof that cyanosis and jaundice are related, that the system of early detection in the workshop then being introduced has been a sheet anchor in combating toxic jaundice.

The peculiar pallor or grey blueness of the countenance of these people which simulates anæmia is *not anæmia*, as Dr Parkes's results, and our own show: it is the altered colour of the blood showing through the skin—in other words, like the ashen blue lips, it is cyanosis. The only other member in our triad of symptoms given last October is "and *perhaps* a faint trace of yellow on the conjunctivæ, the rest of the skin showing no icterus."

When these are observed the patrolling surgeon stops and questions the worker, and then he may hear of abdominal pains, giddiness, sleepiness, breathlessness, sickness. He may or may not elicit this history according to whether the worker feels like resting or going on with work; if the observer be wise he will act mum[my], on what he saw before he disturbed or questioned the worker.

It is out of the question to wait till general jaundice develops, and the first faint trace on the sclerotics is valuable as confirming the cyanosis. One must not wait for deeply yellow conjunctivæ before turning off, it is too dangerous.

We are well aware from having seen them that there are workers who can go on for months with deeply blue lips and never complain, just as there are people who can live for years with serious valvular disease of the heart. There is a chemical compensation in these cyanosed people and they possess resistant liver cells and red

marrow cells, but they are in a danger zone, and the sooner they are weeded out from T.N.T. and put on to other work the better.

Conversely, there are cases where, without any cyanosis so marked as to have attracted attention, jaundice had appeared *apparently* as the first symptom. It is here to be remembered that some skins show cyanosis more readily than others, and that the same poison in different individuals may hit the two types of cell, viz. : (1) red blood corpuscles and hæmatoblasts on the one hand, and (2) liver parenchyma on the other, in varying degree. This is well known for other toxic substances.

While the cyanosis in such cases was not apparent, we have little doubt, for reasons already given, that it was there, and would have been found had it been carefully sought for by blood examination.

On the other hand, there is no question of the frequent association of cyanosis and jaundice, or of the large number of cases where cyanosis appeared first, and later the jaundice.

Several cases have been sent off work for cyanosis and minor T.N.T. symptoms and have developed marked jaundice at home. In other cases, accompanying cyanosis and the minor symptoms there has just been the faintest trace of yellow on the sclerotics, and a few days after, the patient being at home in the interval, there has been profound general jaundice developed, leading in several cases to a fatal result.

One difficulty is the small number of cyanosed cases which go on to jaundice, but widening the outlook on the field of medicine affords parallel cases. Chronic alcoholism, for example, is, like T.N.T. poisoning, a prolonged chemical toxic action, but how few chronic alcoholics pass on into cirrhosis of the liver ? Lead poisoning is a slow chemical effect, but how many lead workers, with the blue line on their gums, pass on to the other classic symptoms and to death from lead poisoning ?

Another point urged against the relationship is that, while cyanosis can be produced by the exhibition of *pure* T.N.T., it is not possible as a result of chronic poisoning in animals to produce the T.N.T. effects on the liver.

In reply, we would say that we have actually produced these effects as already mentioned in one rabbit by administration of pure T.N.T. where there was marked jaundice, and in addition the liver afterwards was examined for us by Dr. Turnbull, who described the effects as similar to the early stages of attack on the liver in human cases. In two other cases of experimental pure T.N.T. poisoning, also in rabbits, well-marked liver lesions of similar type were obtained but not accompanied by jaundice.

It is questionable whether a larger number of positive results than this ought to be expected amongst the numbers of animals experimented upon. As every pharmacologist knows, it is notoriously difficult to re-produce chronic pathological lesions experimentally in animals by the use of drugs. The adjustment

of the dosage and its variation with the duration of the experiment are very difficult to accomplish with the nicety required.

Moreover, we know from our workshop results that for several hundreds of people daily exposed chronically to T.N.T. only one or two develop jaundice. How many positive results may then reasonably be expected amongst two or three dozen animals? Nor can the results be hastened by administration of heavier doses, because that only throws over from chronic into acute effects, and does not reproduce the requisite conditions. In how many cases has alcoholic cirrhosis of the liver been reproduced in animals, although it has often been attempted?

(vi) *Cases Showing Intimate Relation between Cyanosis and Jaundice.*

Next we should like to relate the cases which caused us to adopt the view that cyanosis and jaundice were intimately connected, and to advocate as a result early detection in the actual workshops.

Case I.—Recorded by B.M.—W.O. It was while working daily at ... in September, 1916, that my attention was drawn by the late Welfare Supervisor, Miss York, to this girl who presented the typical "face" and the peculiar pallor in a marked degree. There was no yellow in her complexion. On questioning, she admitted her appetite was poor, that she had a certain amount of nausea, but had not been sick, and that she had slight abdominal pains, but nothing she added sufficient to stop working her. I told her I was certain she had a mild attack of T.N.T. illness, and that she ought to take a time off work. She started weeping, and said she was the only support of her father, who was aged and unable to work. This conversation occurred on a Monday, and it so happened that there was a four days' munition workers' holiday commencing on the following Wednesday evening. She pleaded to be allowed to continue at work those two days, and as she did not then show any signs of cessation, I let her off going to the factory doctor, but told her if she was no better after the holiday she must not start work again.

Two days later Drs. Legge and O'Donovan visited the factory, and in going round Dr. O'Donovan drew attention to a distinct yellow tint on this girl's skin. I had not seen her between whiles. She was at once sent off home, and I told her she must see me first thing on coming back on Monday after the munition workers' four days' rest. When the patient came to see me on the Monday morning her whole face was as yellow as guineas, and she had a general jaundice all over. She was immediately sent into hospital under the care of the ward sister. At first she did not seem very ill in spite of the deep jaundice, and was quite bright and cheerful. On two occasions when I visited her she talked to me quite intelligently, but a few days later I was told she was worse, and on calling found her delirious, next day she was comatose and died. At the post-mortem examination of the usual changes of toxic jaundice due to T.N.T. poisoning were found. A chronic case from this of evasion and the more T.N.T. illness passing on into toxic jaundice and death cannot well be quoted.

Case II.—Recorded by B.M.—I.S. The above was the first workman I saw in the all important act of catching these cases early, and I gained courage and threw men and supervisors to watch and send out to me any person getting off colour and particularly when pallid and showing sallow like tint. That girl was sent to me by a foreman about a week after the death of W.O. Case I. She was markedly cyanosed on the lips and of pale complexion, but with a very fine smooth skin, and there was a slight but

quite distinct yellow tinge on the sclerotics. I had her go away at once to the hostel and be put to bed. Two days later I saw her and examined her carefully. The yellow on the sclerotics had definitely developed, so that it was quite obvious at a glance to anyone, and there was a faint, but quite definite yellow on the unexposed skin area of breast and arms. Fortunately, things did not go beyond this stage with this patient. In about a week both cyanosis and jaundice cleared up, and the change in complexion was most remarkable; her delicate skin was now white and semi-transparent, with a perfect pink on the cheeks. The change from the muddy, greyish-yellow to this was most striking, and was commented upon by a lady visitor, who had seen her along with me when she was jaundiced, and again a week later when she had recovered.

Case III.—(Recorded by B. M.) E. C., a young girl, one of four, whom I took off on the same forenoon in October, 1916, employed in filling exploder bags with *pure* T.N.T. This is a case which I insist upon, and emphasize as of the utmost importance from the point of view of settling definitely the true causative agency in the poison causing jaundice and proving it to be tri-nitro-toluene itself. The actual T.N.T. in use by these girls was a very pure commercial sample, almost colourless, crystalline, perfectly hard and dry. There was no molten T.N.T. anywhere in their neighbourhood, and no fume detectable, except by a slight bitter effect on mouth and nose. In view of the *intense* bitterness of T.N.T. this sensory effect cannot be taken as indicating the presence of any quantity of fume or dust which might be toxic through inhalation; our experiments cited above disprove this possibility.

There was nothing present here but T.N.T. in *hard solid form.*

I inspected, at first asking no questions, a gang of about thirty girls, and, separating four on one side, by questioning found that they had all had the well-known symptoms of minor T.N.T. illness. I then sent them to the certifying surgeon, who stood them all off T.N.T. work.

A most interesting point is that the gang were all alternating their work, and *all, including these four girls, had only resumed work on T.N.T. that very morning about two hours before my visit to the workshop, after a full week's remission on black powder work quite free from T.N.T.*

Next, as to the symptoms on which I detected these four girls: these were ashen-blue lips and gums, a peculiar pallor of their faces, and in three out of the four cases a slight yellow on the sclerotics. The most impressive appearance was the blueness and pallor, without which one would probably have passed over the slight yellow on the sclerotics. But, as one is ever on one's guard for the first signs of jaundice, when the other signs are there, one looks most carefully at the eyes, and then in many cases sees a faint trace of yellow. One would not "stand off" individuals with little or no cyanosis and pallor on such a trace of yellow alone as these girls showed, *under present conditions of admission.*

Now for the subsequent history: within a week off work three of the four, namely, the one who had no yellow tinge on the eyes, a dark-complexioned girl of fourteen (E. M.), and two of those with a slight tinge (M. and L.), quite cleared up, and the change in colour of lips and cheeks was most remarkably striking.

The fourth case (E. C., fair complexion, sixteen years old), is that upon which I wish to lay most stress as showing the connection between cyanosis and jaundice.

Let it be remembered that she was working on the purest form of T.N.T. used, very much purer than that used for melting and making any form of amatol. When she was detected by me she was cyanosed, pale, and had a just definitely detectable tinge on the sclerotics, but no general jaundice on unexposed parts of breast or arms. I sent her, like the others, to the certifying surgeon, who "stood her off" like the other three, and sent her into the nursing home. Two days later I called and saw her, when she was jaundiced quite distinctly all over the body. Again I saw her a week later when the jaundice was fading, but still distinctly

present. The cyanosis and pallor had by this time almost disappeared. The jaundice cleared in about three weeks' time, and the patient recovered.

This case was certified to the Home Office as a case of toxic jaundice by the certifying surgeon, October 15th, 1916.

Case II.—Recorded by B. M. and G. A. W. R. R., aged fifty-five, male. Employed in weighing T.N.T. in Press House. Not near any melted T.N.T. as none is used in the entire building.

The material which this man was roughly weighing out in an ordinary pair of grocer's scales, while not perhaps so pure as that used by the girls described in the previous case, was hard, dry, scaly T.N.T., and would not on the whole contain any appreciable amount of impurities.

He was detected by us on the afternoon of November 11th, 1916, on appearances only. He was then markedly cyanosed and pallid, and had a quite distinct icterus on the conjunctivæ and a slight general one on the skin.

Only on questioning him did he state that he had suffered from flatulence and pain in the abdomen for the last two weeks, and that he had lately seen the Factory Doctor and been off work for a week since when he had been back at work for ten days.

He had no intention of going to see the doctor because he had had this week off so recently, and we had some difficulty in arranging him to the fact that he was seriously ill and must leave work and go to the doctor at once.

He was sent to the N. Infirmary by the certifying surgeon, and we saw him there two days later. He was then deeply jaundiced, but did not complain much, and talked intelligibly.

A week later we saw him when he was still deeply jaundiced, drowsy, and dyspnœic, and unable to answer questions, and our prognosis was that he would not recover. He remained like this for a few days, and then began to get better, and finally recovered.

He was certified to the Home Office as a case of toxic jaundice, date November 9th, 1916; occupation, weighing T.N.T. in Press House; duration of employment, three months; severity, severe; remarks, vomited November 5th, continued at work till detected by Surgeon November 9th, still declared he felt all right.

This case illustrates again the connection of cyanosis and early jaundice.

Case III.—Recorded by B. M. and G. A. W. R., male, aged 32. Trucking to cylinders, Melt House. November 29th, 1916.

We thought this case in a curious way—just one day before we went to the factory concluded.

We were endeavouring to determine the average intensity of the reaction of T.N.T. in the urines of the workers in a large shop, such as this one. We had found by experience that there was great delay when workers were asked to give a sample of urine; a few refused, others made excuses and said they had none. So provided with the necessary pans, funnels and bottles, we proceeded to the men's latrines and each man turned up, we simply asked him to urinate into one of our pans instead of into the urinal. We got the twenty-four urines we required in about as many minutes.

We took notes of the condition and employment of each man who contributed, and K. was one of these. He was markedly cyanosed on the lips, and also showed jaundice, not only on the eyes, but on chest and abdomen.

He seemed greatly surprised when we told him he was seriously ill and must stop working and go to the Factory Doctor at once. In fact, it was only by threatening to report him to the Foreman that we got him to promise he would go. The specimen of his urine showed a high content of altered T.N.T. (equivalent to 3 on our scale).

We did not ourselves see this patient again, but he was returned to the Home Office by the Certifying Surgeon of the Factory as a case of toxic jaundice, and we quote the following from the monthly returns of February, 1917:—K., male, 32; date of disablement, 29th November, 1916; precise occupation, filling under cylinders; duration of employment, 4½ months; severity, slight; remarks, October 17th symptoms, severe gastric catarrh; suspended until October 31st, when allowed to resume at cylinders. Again suspended November 29th (this was the point of our intervention) until January 3rd (*i.e.*, for five weeks), when returned to another part of factory. January 10th, suspended for continued signs of jaundice. January 16th slight conjunctival jaundice. At suspension on November 29th his whole skin was washed with acetone.

It is clear that this patient had minor T.N.T. illness prior to appearance of jaundice.

It is interesting that in this history supplied from the Factory to Home Office there is no mention of cyanosis, either in the period of his illness prior to our detection of him, at this period, or later. Yet when we sent him off on November 29th he was markedly cyanosed. This is not said in order to throw blame on any observer, for cyanosis at the early stage in these jaundice cases may be too common to mention.

Summing up on these five cases, which are our own personal experience and detected in the actual workshop when they had no intention of reporting ill, we would point out in the first place how clearly they demonstrate the value of early detection, for we feel certain that one, if not more, would have perished but for our detection. In the second place, the universal presence of cyanosis in cases caught and observed in the initial stages and the importance of this sign in attracting early attention.

Case VI.—(Recorded by B. M.) F. W. Weigher to Pellet Press.

This case occurred at a considerably later date than the previous five, and is here recorded to show the fallacy of accepting without thorough investigation negative evidence as to absence of signs and symptoms other than conjunctival jaundice.

I was down at the factory where this fatal case of toxic jaundice occurred, endeavouring to perfect a mechanical contrivance for keeping the girls' hands out of contact with the powder in one of the most dangerous forms of T.N.T. employment, when it was reported to me that one of these very girls was then in hospital seriously ill with T.N.T. poisoning.

I had been told by the Works Manager and the Welfare Superintendent that the very first thing noticed was the jaundice in the eyes, and this without any premonitory warnings, thus showing the impossibility of catching early some of these cases. The same evening I visited the Factory Doctor and heard the same tale. I asked specifically if cyanosis or other signs of T.N.T. illness had been observed, and was definitely answered in the negative. The doctor told me he had seen the girl on his usual Wednesday visit three weeks previously. The only thing he detected was a faint yellow on the sclerotics, and, cross-questioning, failed to elicit any admission of symptoms of T.N.T. illness. He did not send her off work, but said she was to be kept under observation. On the following Monday she was sent to him with much deeper jaundice on the eyes, and with slight general jaundice, and was then sent to the nursing home.

Here, then, seemed to be a typical case of jaundice occurring first, unaccompanied by cyanosis and other minor symptoms, the sort of case upon which those medical officers rely who hold that (1) minor T.N.T. illness and cyanosis, and (2) toxic jaundice are distinct clinical entities.

Being on the spot, I determined to examine thoroughly into the evidence of this seemingly foudroyant case, and I interviewed her relations, her co-workers in the same shed, and her lodging-mates. These, without any leading questions whatever, all concordantly volunteered the informa-

tion that her husband gave him for safety a fortnight before that she had complaints of giddiness, had shown symptoms and headache, and in the last few days had been breathless and scarcely able to walk. These facts were also brought out at the inquest which I attended, and it was quite clear that the casualties had been preceded by symptoms and all the underlying symptoms of minor T N T disease.

There were two obvious things which appear to have contributed to these symptoms having been missed by Doctor and Welfare Superviser. In the first place, the girl was most careful and obedient to all Factory Rules, and constantly and most anxiously were her supervisor, so that Supervisor and other responsible people could be able to see her lips, illustrating another danger of cigarettes, for the same statement has been made at inquests on other fatalities at the same factory. In the second place, the temporary suspension at this factory at this period consisted in sending out the girls in batches from their work to see the doctor, as no call done in several other factories. This involved, as I have again and again tried to explain, delicate nervous ends. If examination of the lips and palms of faces are to be detected it must be done in the workshop and when the workers are working. The excitement of going off to see the doctor, going out of the workroom in presence of co-workers, and going home and waiting at the doctor's examining room, in a nervous and trembling person such as this girl appears to have been acts the heart beating more rapidly, upsets the vaso-motor balance and causes flushing of face and lips.

This appears to have been what happened in this case, the same reticence, and perhaps a fear of being turned off work when she did not feel herself ill enough for that, seem to have complicated the situation and made her deny to the doctor's question even the scanty information she gave in her lodging and at the factory.

The following are the facts of the inquiries in this case. —

On the Sunday morning the day before the girl's death I visited her at the Nursing Home and found her paralysed, delirious, and extremely ill. The Matron told me that she was jaundiced both as eyes and skin generally when admitted three weeks previously, but she had not noticed whether or not her lips were blue.

When I asked if I could see any of her relations I was told they were in another room, and I went at once and interviewed them.

They were a brother and three sisters. I simply asked them to tell me anything they had noticed in their sister before she was taken ill. She had her home at C. (about ten miles off), lodged at L., and went home to see her people usually on the week-ends. One sister told me that they had noticed how tired and sleepy she was on the two weeks previous to her illness. That she went to sleep in the afternoon—a thing up-sense old. At this point she was interrupted by one of the other sisters, who said: "And I noticed, by the way that her lips had gone". [The underlined sentence (italics exclusively editorial) was spoken in such a way that I had not got any question to any of them except the original one stated above.

Thereafter, after an interval, the girl—M. K.—who was the deceased girl's eldest and brightest sister. This girl told me her friend had got trouble at the home, and that she went with people. [The italics were a second emphatic statement and an interesting one as will transpire later, but had not attracted me, but other people in the workroom did, and had they been questioned had T N T disease arisen her evidence had obviously got a bearing on the inquiry.

The landlady also thought she was ill. I saw a jolly, rather fat girl, who complained of, and looked pale and sweaty mind. Her appetite had gone, and when her landlady and others threatened to tell the Welfare Supervisor the latter promptly took fright and said she had no pains and would not go to the doctor. She was conveyed home at once at work and at home to bed, empty, and shortly died.

Confirmation of this statement was given at the inquest.

The deceased girl's sister, N. W., at the inquest stated again that she had noticed the blue lips and mentioned it to her two other sisters, who agreed and said she was also short of breath. She could hardly touch food, and was very sleepy, but persisted in saying she was all right, only short of breath.

A girl working on the same machine with her gave evidence that the deceased had complained to her of giddiness, and she had noticed her lips had gone blue a week before, and on the Saturday afternoon previous to leaving off work she had been giddy and trembling.

Clearer proof than the above of cyanosis and oxygen-dearth previous to the onset of the jaundice could scarcely be adduced.

V. Prophylactic Measures.

(i) *Early Detection of Cyanosis.*

The researches and observations recorded above seem to furnish not only a sure guide for the introduction of precautionary measures, but show how unnecessary expense and fruitless employment of skilled labour in such a time of dearth may be avoided. The importance of early detection of the preliminary stages of T.N.T. poisoning has been throughout insisted on in this report and the methods have been indicated by which early detection may be ensured.

(ii) *Ventilation.*

We believe that if a dust-extraction experiment be made beforehand, as it obviously ought in each case, it will be found that many proposed schemes of forced ventilation need not be carried out. The vast majority of T.N.T. workshops are clean, airy, naturally well ventilated, one-storey buildings, in which our analyses, as far as they go, show that the quantity of T.N.T. dust is negligible.

(iii) *Prevention of Skin Absorption.*

The knowledge that the main absorption occurs through the skin of the hands indicates three lines of action, namely, (1) keeping all that the hands can touch clean, (2) protecting the hands, (3) detecting those hands which are permeable and keeping their owners off T.N.T. work.

1. *Provision of Shell Filling Machinery.*—The realisation of the skin danger has produced a remarkable change for the better in recent months in many factories; this has far-reaching results in other directions as well as the hygienic one. The provision of machinery for shell filling is, of course, considered a matter of the greatest urgency. Not only will it enable each worker to avoid much hand contact with T.N.T., but in addition the greater speed attained will allow very large numbers of workers to be set free for other national work, and lead to great saving. Another point which may be suggested is that the most intimate relation should be developed between the different factories, so that the quickest method for a given operation used in any one place may be installed rapidly and efficiently by means of demonstrations given to the others.

2 *Protective Clothing, Gloves and Boots.*—The most important skin area to protect is that of the hands, for although there is staining of face and hair, the actual amount of T.N.T. falling on these areas is small, and we have shown that it is only when the unprotected hands are used to carry on the manipulations of the workshop that any appreciable amount of modified T.N.T. appears in the urine.

The most obvious first thought is to cover the hands with impervious gloves, and we have spent much time in designing gloves and glove attachments of various kinds and of different materials, these all broke down in practice. We could protect ourselves and did do so for an entire week while working in a shop, and we could protect workers under experiment whom we ourselves arrayed and disarrayed from their workshop costumes, but our best attempts to drill a band of workers to carry out these operations for themselves failed. Once the T.N.T. gets underneath the glove, as it does with all workshop gloves hitherto tried, they are worse than useless, for the inner surface of the glove holds the powder in closer apposition to the skin, while the perspiration makes it soft and damp, and the glove and the perspiration together make the skin soft and permeable. So that, except for very rough tasks which hurt the skin of girls' hands, bare hands are preferable to gloved ones, and in the few cases where gloves must be worn they should be loose thick leather ones.

The other portions of workshop clothing ought to be arranged to protect the skin, and the clothing of T.N.T. workers is rightly kept apart from that of other workers. Often a needless amount of contact with T.N.T. is contracted in the cloakrooms from careless handling of boots and costumes by the workers. Alternated workers have two sets of clothing, one for "off" and one for "on" T.N.T.; these ought to be kept in separate cloakrooms with separate access, and inspection made that no worker dons "off" clothes with his or her own home clothing contaminated with T.N.T.

Operations with damp amatol powder leading to damp clothing are now fortunately much more rare than formerly, thanks mainly to the appreciation of the fact that illness is produced from skin contact and that accordingly the operations must be conducted with as great cleanliness as possible. For this reason it is only in a few instances that overalls or aprons of waterproofed material need be employed, and an overall or blouse of boiler house cloth is becoming very common in the factories and is very serviceable for its purpose. As to the make-up, the "bloomer" suit has become very popular for women munition workers and is much to be preferred to any form of skirt. A two piece suit consisting of bloomers and a blouse is now in very general use. The bloomers ought to be made shorter in the leg than at present and to end over, *not in*, long Wellington boots. Such boots were

introduced at certain factories and have proved a great success. The skin of the girls' feet, which used to be quite yellow from T.N.T. absorption, is now clear of it.

At three large national factories visited by the writer quite unsuitable footwear was being worn by all the girls, in the form of low, open shoes, leaving the dorsum of the foot covered only by a thin stocking and so exposed for the T.N.T. to fall upon it. This is quite an unnecessary area of absorption to add to hands and face, as is now generally admitted.

3. *T.N.T. Solvents and Protective Varnishes for the Skin.* Prolonged experiments have been carried out by B. M. and C. A. W. at an explosives factory on methods for protection of the skin, either by T.N.T. solvents, or by protective varnishes to keep the powder off the skin of hands and face.

The results have been most interesting, and, if properly applied, ought to ensure a great degree of protection, not only to T.N.T. workers, but to "tetryl" workers also, who have suffered greatly in the past from dermatitis.

Our thanks have been expressed to the directors for permission to carry out the work and for much kindness during its progress; we have also expressed our indebtedness to the works manager, and to the nurse at the works, for much valuable assistance.

Xylene Washing of Skin.—As washing of the skin with acetone, a solvent for T.N.T., had, in the cases of workers being taken off work on T.N.T. with severe symptoms of illness, given beneficial results in the opinion of several observers, an experiment was started to observe the effects of daily washing with a T.N.T. solvent upon the colour of the hands, and reaction in the urine, of a band of T.N.T. workers.

The underlying idea of the experiment is that, as T.N.T. is practically insoluble in water, the ordinary ablution with soap and water at the end of a period of labour does not remove the minute particles of T.N.T. from the skin, and thus the worker is not only exposed to the poison during the hours of labour, but the absorption from the reservoir in and on the skin goes on during the hours of recreation and repose in the case of the susceptible worker.

It was thought, therefore, that if the hands were soaked in a good solvent for T.N.T. at the end of the day's task, a good portion of this T.N.T. could be washed away and the susceptible worker be spared a considerable amount of absorption during the rest period. This would show itself objectively in a decrease of the stain on the hands and in a diminution of intensity of the characteristic reaction in the urine.

A band of twenty-four girls was accordingly selected, and after determining the degree of intensity of the urinary reaction for T N T, they were instructed to wash their hands each day on leaving off work with a mixture of the xylenes recommended to us as a good T N T solvent by Dr G. Barger after experimentation with several solvents. Acetone and several other solvents are barred out by their present scarcity.

The results proved disappointing. The solvent appeared to diminish somewhat the depth of colouring of the hands, but the degree of urinary reaction during the fortnight on T N T seemed to run on its usual upward course just as if no washing had taken place. The figures are given below. (Appendix D.)

It may be that the result is due to the petroleum solvent used having made the layers of epidermis more permeable and having caused a more rapid ride through into the system at the time of washing. The solvent did actually remove all T N T from the outer layers, as shown by the failure of the alkaline shaded test after the use of the solvent.

The failure of this experiment does not necessarily rule out the recommendation that persons seriously ill with T N T poisoning, or actually jaundiced, should at the time of their removal from work and contact with T N T have their skins thoroughly cleansed whenever possible with acetone. Their case differs entirely from that of persons who continue to be exposed to T N T daily and they ought at once to be cut off as completely as possible from all contact with T N T in clothing or skin. Experience may show whether the acetone treatment is of value for such cases.

Protective Varnishing of Skin with Casein Varnish.—Our attention next turned in the direction of coating the skin with some impermeable varnish before starting work, which could be washed off or removed by solvents at the end of work, so carrying away any T N T with it.

An impermeable varnish, insoluble in water, was first tried in the form of a solution in appropriate solvents of acetate of cellulose, but this varnish peeled and partially cracked off, exposing the skin, and a similar fate fell upon "collodion and suskin" varnishes.

A water soluble varnish suggested itself next, which would simply wash off with water at the conclusion of work and at the same time wash off the T N T along with it. At this point Mr Arthur Whitnell was consulted, and he helped us materially by suggesting several modifications of water-soluble varnishes, amongst them an adaptation of the "casein varnish" of the British Pharmacopœia made so as not to be fat- and oil-free. This preparation was made for us by a firm at Nottingham, and is the result of several weeks' trials at factory B, and gives us most excellent results. An experiment on a larger scale is now being made at another factory, and several factories in different parts of the country are now commencing to use it.

Experience may indicate in time a better "body" for the varnish, and it may be necessary to work out something which will resist better in hot weather and not be removed by perspiration; but the experiments have already shown that for dusty types of T.N.T. employment, such as "exploder bag" work, protection of the skin of face and hands by a varnish is feasible, and that when the skin is thus protected there is a great fall in the amount of T.N.T. in the system, as shown by the urinary test.

The improvement is visible to the girls themselves and to the nurses. Some girls stain much more heavily on face and hands than do others, and we have taken purposely the very highly stained workers and seen the stain under the use of the varnish almost disappear from face and hands in about a fortnight to three weeks; at a later stage the urinary reaction falls off. Details are given below. The preparation also protects against "Tetryl" stain and has been found of great service in "Tetryl" dermatitis. It is not unsightly in use, as it sinks into the skin and disappears. It has at present one defect, that when kept it tends to thicken, and then sometimes lathers and does not become invisible on the skin; when this occurs some of the girls object to applying it. Also, on a few very delicate skins there have been complaints of slight tingling after its application. But in all cases it protects, and a slight tingling or its showing on the face is a small discomfort compared to a dermatitis.

(iv) *Removal from T.N.T. Work of Persons Specially Susceptible to the Poison.*

Some difference of opinion appears to exist as to whether the same workers ought to be allowed to remain for many months engaged upon T.N.T. work on account of the danger of the prolonged period of absorption, or whether such individuals have proved themselves insusceptible and ought to be cherished and retained.

The answer depends on the health history of the individual. A person who has been upon T.N.T. work continuously for, say, a year or more, and has never shown any signs of T.N.T. illness—and we have examined many cases of both sexes of whom this is true—such a person is a most valuable asset to a factory, and should be preserved most sedulously.

On the other hand, a person who has been ill more than once during a working period of, say, five or six months, with minor T.N.T. illness and been "stood off" work on this account, should be watched most carefully and "stood off" at once at the appearance of any considerable cyanosis. In fact, if we had our will we should gradually remove these people who are evidently absorbers and susceptibles, for there are plenty of non-susceptibles to carry on all the T.N.T. work.

Our experiences leave us little doubt that an important factor in the recent improvements is the gradual operation of a natural "salting out" process, whereby an industrial "selection

of the fittest " *for this particular task* has occurred. This natural tendency, management and medical staff, working together, should try to accelerate by removing the susceptibles as rapidly as the exigencies of labour supply will allow. To assist them in this an endeavour should be made by those in charge of labour supplies to direct a strong tide of oncoming labour towards T.N.T. Such an effort will become more effective as the conditions of T.N.T. occupations become healthier.

There is a natural hygienic stream which is tending to remove susceptibles all the time, and to retain insusceptibles. If a worker is healthy on T.N.T. the good wages will retain that worker. He or she will have no fear of T.N.T. illness, and will scout the idea of danger to all hearers inside and outside the factory; this we have seen personally in hundreds of cases. On the other hand, if the worker is a susceptible and is feeling ill and miserable while at work, and has frequently broken time from minor T.N.T. illness and been off on " compensation pay," then that worker is an unsound economic proposition from the factory's point of view.

The latter type of worker will naturally tend to clear away from T.N.T. labour, while the former type will stick to it, and thus a factory which has been operating for many months will possess a far better ' salted " set of workers than one just starting.

This is clearly seen where the illness and irritation caused by a work substance is more acute and gives more discomfort and suffering—a work substance, for example, causing such effects is " tetryl," which sets up in a large proportion of beginners an acute inflammation of the skin and mucous membranes, and œdema under the eyelids. Some people become inured in a few days, others never do, and after suffering from severe dermatitis for weeks have to give the work up. Fortunately there is no constitutional attack as in T.N.T.

When a new " tetryl " workshop is started with an " unsalted " set of workers there is always a busy time for a week or two for the medical staff—in some cases the whole shop has had to close down for a few days. Then for some weeks or months there is a considerable amount of dermatitis, which finally dies down almost to zero.

Those who have been very badly affected have soon " had enough of it " and go away to other work, " new starts " come on and take their places. Gradually those who do not acquire immunity clear away, and the trouble drops down to occasional cases.

The same thing has doubtless been happening in a less obvious way amongst T.N.T. workers.

A prophylactic measure which has received a very wide spread application in the campaign against T.N.T. poisoning is that known as " alternation of labour," a plan which had been employed in pre-war times in other occupations in which the workers were subject to absorption of poisonous substances.

The writer was at one period a hearty supporter of this policy, but recent events have caused him to alter his views, not because he does not still consider that alternation is good for the individual worker, but because there are other objections to it from the point of view of the workers *en masse*, and from the national aspect of economy and output, and because there are other means by which the end in view can be achieved with equal certainty and at much less cost in every way.

The principle of alternation of employment is that double the number of workers should be employed to work upon the dangerous material and relieve one another of half the risk by working for equal alternative periods of a week or a fortnight. There is certainly a distribution of risk to the individual in such a policy, but in the mass, for reasons which will be disclosed, the exposure is much more than doubled.

The most important point to bear in mind is that all our experience teaches us that there is a marked idiosyncracy in the incidence of T.N.T. illness, that some individuals with constant exposure month after month have never been ill, while others have died as a result of one fortnight of exposure only.

Any system of alternation, if the output per individual were equally good, would obviously expose just double the number of susceptible individuals to attack, but the statements of managers as well as factory returns show that the output is not nearly so good under alternation as under continuous employment, and so the total number of exposures to T.N.T. poisoning as a result is correspondingly more than double.

Again, the risk of exposure of each individual under alternation is by no means reduced to half of what it is under continuous employment. This is shown by our urinary estimations upon alternated workers given in Appendix A. Tables IV. V. and VI. by our clinical experience on workers returning after a week's "off" employment ill with T.N.T., by outbreak of T.N.T. illness in many cases in the records a fortnight or more after going "off" T.N.T. work, and by our knowledge of the T.N.T. reservoirs in skin and clothing. Compare the figures given in the Appendix which show the clearance effected in the urine by four days' holiday, spent probably in fresh gala clothes, with that effected by a fortnight on alternated work ("off" T.N.T.). In the latter case the workers are perhaps in contact with clothing soiled during the "on" period, and with soiled woodwork of boxes, trucks or shells.

In the earlier months of the trial it looked as if the statistics showed that there was a great balance in favour of alternation. Those factories where there was alternation appeared to be healthy, while those which did not alternate had the heavier incidence. But it does not appear as if the figures of more recent months substantiated this result. Since other improvements have been introduced into certain of these "continuous" factories their records have become quite as favourable as those of the "alter-

nated" cases; and now looking back at the past, most of those who inspected the whole system of factories would have to admit that the better conditions which existed formerly at the "alternated" factories might in reality have been due to precautions other than alternation, precautions which were not at that time taken at "continuous" factories.

It is the almost universal belief of works managers that the economic price to be paid for alternation in efficiency and output is a very heavy one, and amongst the best workers, especially where bonuses are paid on piecework, it is commonly detested.

It may be said that this question of output has nothing to do with the hygienist's task, and at first sight this would appear to be true, but in any case it is a most important national question, and further consideration shows that it does directly concern the hygienist. For the speedier the rate of working the less the number of hands required and the smaller the number subject to the absorption of poison. The more skilled a worker becomes the less mess that worker makes, and less mess means less infection for everyone concerned. Also, if speed of working is increased, say, 50 per cent.,* from the skill that comes from continuous labour, then two-thirds of the operatives will do the same amount on a shift, and the double set of "off" and "on" workers will not be required. Thus on continuous working on such a basis there will only be required *two* workers instead of *six* as on alternation who will run the risk of T.N.T. illness and be paid the higher rate of T.N.T. wages. Also when the six workers are half "on" and half "off" T.N.T. work they are a great deal more than half their time subject to T.N.T. absorption for the reasons already given.

What, then, is it proposed to put in the place of alternation? The reply is, increased medical care of the smaller number of workers and increased amount of "sifting out" or removing the susceptible *permanently* from T.N.T. work.

VI. Treatment of Cases.

It ought in the future only to be in rare instances that cases pass unnoticed through cyanosis into toxic jaundice. When this has occurred, as well as in all severely examined cases, the first essential is afterall to see to it that complete rest is given from all sources of T.N.T. For this purpose it is not sufficient simply to give instructions to the patient and send him or her home to relatives. These people and their friends have little realisation of the seriousness of their illness, and for this reason have made light of jaundice for days in cases which have subsequently proved fatal. Nor is it generally realised how difficult it is to make a

* This may be assumed as conservative estimation, but the effects can be obtained in practice of the variations of a surprisingly marked. One worker manager has assured me that at his works (London area) alternation, and thus the workers, is continuous work, no period intervening between shifts, but with a day shift half as wide and eight shifts a week.

clean cut-off from contact with T.N.T. It was only continued experimentation on the effects of (1) week-ends, (2) holidays, (3) alternation, and (4) the study of the decline in the urinary reaction in patients "stood off" T.N.T. work, which taught us this lesson. The T.N.T. is carried home on hair and hands and clothing, so that not only are these people subject to contact during working hours, but their homes, or lodgings, and their furniture and bedding become contaminated with it. As a result we have seen the skins of infants and little children in the homes, who have never been near the factory, deeply stained from contact with the persons and clothing of their parents, and the hair of wives stained the characteristic auburn brown from powder communicated from their husbands. Also we have seen the stain on bed-sheets and pillows.

This must always be borne in mind in treating severe cases of T.N.T. poisoning, and especially when any jaundice is present. As a rule, such cases ought never to be treated at home, but in a hospital by a physician possessing some experience of T.N.T. cases.

It ought particularly to be emphasised that this is true of the *first few days of incipient jaundice*, for at this stage the case looks less serious than it does later when the jaundice deepens, and so the physician may be inclined to risk these few days, to see how the case develops with home treatment and visits to the consulting room. But these few initial days are the all-important ones, far more so than those after the skin becomes deeply jaundiced, for then the physician can but watch and wait, and is powerless to give much help in the struggle. The first appearance of jaundice shows that the compensation described above has been surpassed, a stern fight is going on between processes of degeneration and regeneration in the hepatic parenchyma, and degeneration is slowly gaining so that there is no longer enough sound tissue left to carry on the metabolic functions. A little longer attack by the poison, and the descent will soon become more rapid. This is the point at which the prompt action taken by the physician in completely cutting off the supply of poison makes all the difference.

The patient should be removed at once from factory and home surroundings to a nursing home or hospital. Every stitch of clothing which has been near T.N.T. or in contact with the patient's body previous to the purification now to be described should be removed. The patient should then be given a warm bath, dried, and the skin, wherever it has been exposed, thoroughly cleaned from all trace of T.N.T. by scrubbing with pledgets of cotton wool soaked in acetone or ether until no pink colour is shown with alkaline alcohol. Special attention should be paid to palms of hands. The nails should be cut short and carefully manicured, and the roots of the hairs cleaned, especially on the scalp. The patient should then be put in bed in an airy position and given a purgative. The bowels must be moved as soon as

possible and kept open. The urinary secretion and perspiration ought then to be stimulated by a simple saline mixture, and this should be kept up for two or three days until Webster's reaction is no longer obtained in the urine, and the test remains negative even after this diuretic and diaphoretic action is discontinued.

Fresh vegetable food and fruit are desirable and alkalies should be given as there is a certain amount of acidosis in some cases.

Where, in slighter cases of cyanosis, the patient is not kept in bed, an open air treatment is best; there ought not to be so much exercise as to make the patient breathless, but moderate exercise and sitting or reclining in the open. In a few days these cases clear up as the met-hæmoglobin breaks up.

If any cyanosed case be allowed back on T.N.T. work, he or she must be carefully watched and a recurrence of the symptoms ought to determine the matter. The patient should then be given a permanent discharge, and no attention paid to the request which is so often made that they should be allowed to continue at the work.

No person who has ever had toxic jaundice is under any circumstances allowed back to T.N.T. employment or work connected in the same factory with T.N.T. labour.

APPENDICES, TABLES, AND PROTOCOLS OF EXPERIMENTS.

APPENDIX A.

EFFECTS OF CESSATION OF WORK (1) AT WEEK-ENDS, (2) HOLIDAYS (FOUR DAYS) AND (3) AT PERIODS OF ALTERNATION OF LABOUR, UPON THE AMOUNT OF T.N.T. PASSING THROUGH THE SYSTEM.

The figures stand for the judged intensity of colour in the Webster test upon an arbitrary scale, and are in many cases the agreed judgment of two observers (T. A. W. and G. A. W.) using the test daily so that they are comparable amongst themselves.

TABLE I.

Effects of week-end rest at Messrs. —— from Saturday, September 23rd, to Monday, September 25th, 1916. All girls.

Girl.	Reaction.		Girl.	Reaction.	
	Before.	After.		Before.	After.
			Brought forwd.	92	66
1	4	3	29	4	1
2	3	2	30	1	2
3	4	4	31	4	1
4	5	2	32	3	0
5	3	1	33	4	2
6	4	2	34	4	1
7	3	0·5	35	3	2
8	3	4	36	4	1
9	2	2	37	3	2
10	2	5	38	3	0·5
11	2	2	39	5	4
12	4	4	40	3	2
13	4	2	41	4	2
14	4	3	42	3	1
15	3	1	43	5	1
16	3	3	44	3	0
17	3	1	45	2	2
18	4	3	46	4	2
19	4	2	47	3	0·5
20	3	3	48	5	4
21	1	3	49	3	1
22	5	3	50	5	3
23	3	2	51	2	0
24	3	1	52	2	0·5
25	3	1			
26	3	3	Totals 52	174	101·5
27	3	0·5			
28	4	3	Av. Rn.	3·3	2
Carried forwd.	92	66			

Notes.—The intensity set down at the value 0·5 is what we customarily called a trace, and is equivalent to what would be obtained when 5 to 10 milligrams is swallowed, and a little less than is obtained during a shift in the case of a careful worker with completely protected hands. It is to be observed that no worker was clear to this extent on the Saturday, and that only three were clear completely on the Monday and five others

down to a trace, while the average reaction fell to two-thirds of its previous value. At this period in our investigations we had not yet realised how easily specimens might be accidentally contaminated if passed at the factory closets, and so these may have been a certain number of contaminated specimens amongst those which would raise both averages.

TABLE II.

A fortnight later a second set of samples was collected. Each girl was given two bottles with her name on them, and asked to collect one specimen as soon as possible after reaching her home (on the Saturday), marking the time on the bottle, and to take a second sample on Monday morning after rising and bring both to the factory. Meanwhile we had devised a method for detecting and estimating contamination, and in any case giving a high value this correction was applied where necessary. (See text p. 17.) The results were as follows:—

EFFECTS OF WEEK-END REST AT MEALS. FROM SATURDAY, OCTOBER 7TH, TILL MONDAY, OCTOBER 9TH, 1916.

Girl	Reaction.		Girl	Reaction.	
	Before.	After.		Before.	After.
			Brought forward.	46	14·5
1	2	0	24	0·5	0·5
2	3	1	25	2	0·5
3	2	0·5	26	2	1
4	2	0	27	0	0
5	1	0·5	28	0	0
6	2	0·5	29	1	0·5
7	1	1	30	2	0
8	2	1	31	1	0·5
9	0·5	0·5	32	1	1
10	0·5	0·5	33	1	0
11	1	0	34	1	1
12	1	0	35	0	0
13	1	1	36	0	0
14	3	1	37	0·5	0·5
15	3	0·5	38	0	0
16	3	0·5	39	2	0·5
17	1	0·5	40	1	0
18	3	1	41	0·5	0
19	3	2	42	0	0
20	3	1			
21	5	0·5	Totals 42	61·5	20·5
22	1	0·5			
23	2	0·5	Av. 1·46	1·5	0·5
Carried forward	46	14·5			

NOTE.—This week-end increase shows a much better clearance effect. There were six girls sent at the Saturday and fourteen on the Monday, and in addition five had a toilet only on the Saturday and seventeen had only a toilet on the Monday.

TABLE III.

EFFECTS OF A THREE DAYS' MID-TERM WORKER'S HOLIDAY.

A fortnight was taken for the recording during our visit, to obtain as many samples as possible before and after something from the same girl to get a sample both before and after as the results are given in groups according to intensity of reaction. On the day of return after the four days' rest

85 urinary samples were obtained from as many girls; these showed Webster reactions as follows:—

Nos.	Reactions.
62	Free
10	Trace
10	1
1	2
2	3

Thus there is only an appreciable amount of T.N.T. in the system in 3 out of 85 girls. This is a most remarkable clearance for a four days' rest, and quite eclipses anything given by alternation of labour (see below).

Our returns show that in the course of our routine examinations we had happened to get specimens from 59 out of the above 85 girls on one, two or three days before the holidays. These are given for contrast with the above figures, as follows:—

Nos.	Reactions.
None	Free
2	Trace
13	1
19	2
15	3
9	4
1	Intense

The explanation probably lies in the complete "cut-off" from *all* contact during the four days. On an ordinary week-end the girls live in the same rooms to which they have conveyed T.N.T. on their clothing, they are touching it on their clothing, and probably a good many sleep in day underclothing. A very large number of these girls come to lodgings from homes in healthy situations at a distance, and we know they nearly all went back home for the holiday. They probably all cleaned up smartly and went into gala clothes for the occasion, and also probably enjoyed themselves a good deal in the open air in fresh seaside and country breezes.

The effects are even more striking than the crude comparison of the two sets of figures show; for of the 23 positives out of 85 after the holidays, 8 (which included one of the two reaction of 3 and the only reaction of 2) were passed after the girls had been several hours back at work. The other reaction 3 after two hours back at work, and 7 others were taken during the first day's work. Thus at least 16 of these 23 positives were taken after restarting work. This leaves the position that out of 69 specimens taken before resuming work after the four days' holiday only 2 showed any T.N.T. reaction, and these were "traces."

Tables IV, V, and VI.

Effects of Fortnightly Alternation of Labour on Amounts of T.N.T. in the system as indicated by Urinary Reaction. Carried out at National Shell Filling Factory, ——

Urines were obtained from 76 girls "on" T.N.T. and 76 girls "off," with the object of using the urine test for T.N.T. as an indication as to how far freedom from contact with the poison was realised by alternation.

All the samples were morning urines, since most or all of the T.N.T. inhaled or swallowed the previous day while at work will have been eliminated by the morning. Thus the reactions give a rough indication of the relative quantities absorbed by the skin of the individuals concerned.

The specimens were obtained from 45 girls in the filling sheds (amatol) and from 31 trolleying in the same part of the factory, all having been a fortnight "on" and "off" T.N.T. respectively.

On the exploder-bag side of the factory urines were obtained from 31 girls filling (pure T.N.T. powder) and from 14 cleaning, and 31 at "fuses and gaines," the two latter being "off" jobs; all these had been one

week "on" and "off" T N T respectively. A summary of the results of the tests is shown in the following two tables :—

TABLE IV

SHOWING LIVER REACTIONS IN 76 CASES "ON" T N T

	No. of cases	Weeks	No. of cases showing a reaction of					Mean reaction
			0	Trace	1	2	3	
Filling Shells	15	2	—	6	18	9	2	1 1
Exploder bags	41	1	2	15	14	—	—	0 7

SHOWING LIVER REACTIONS IN 76 CASES "OFF" T N T

	No. of cases	Weeks "off"	No. of cases showing a reaction of					Mean reaction
			0	Trace	1	2	3	
Triddyers	31	2	6	22	3	—	—	0 26
	14	1	8	6	—	—	—	0 11
	30	1	16	14	1			0 13

These results show very distinct benefit from alternation, but they also show that freedom from contact during "off" periods is not so absolute as would naturally be assumed.

The percentages of urobilin showing traces or more of T N T in the urine while "off" T N T are as follows :—81 per cent. of triddyers, 43 per cent. of chemists, 48 per cent. of workers on fuses ; confirming other observations on the possibilities of control of the triddyers with T N T.

At 18, Lindsey's suggestion, 3 rounds of supplies were taken a fortnight from seven triddyers, who in the previous experiment were in the fifties mostly and were then given mixtures of 1 or higher.

Eleven samples were obtained, and the results are tabulated in the next table.

TABLE V

URINES OF 11 WORKERS ASKED AS TO DATE, THE FIRST IN THE END OF THE FORTNIGHT'S PERIOD AND THE SECOND AT THE END OF THE FORTNIGHT'S TRIDDYING.

Urines	Reaction on 19th October, 1916.	Reaction on 29th October, 1916.
1	3	2
2	2	1
3	2	1
4	2	Trace
5	1	Trace
6	2	Trace
7	1	Trace
8	1	Trace
9	1	2
10	1	Light trace
11	2	Nil
	Average 1·8	Average 0·8

These results are instructive, and seem to indicate that those who gave the high reactions when filling are those whose skin most readily absorbs T.N.T., and who are therefore presumably the most likely to suffer from poisoning. It may be that they are simply the most careless individuals, but the well-known fact that some of the fatal cases have been those who have rigorously followed all the hygienic rules seems to negative this suggestion.

APPENDIX B.

Analyses of Factory Air for Dust and Fume by Extraction Apparatus.

The apparatus and mode of using it have been described in the text. The connections will be understood from the accompanying sketch (see Experiment V). The only portion which varied was the piece at the inlet for absorbing the dust and fume. In the first experiment this was a modified U tube with an expanded chamber to facilitate bubbling on the outlet limb; this apparatus was very fragile and was broken when in use for the second time. It was then replaced by the two ordinary U tubes in series, as described in the text, care being taken to test for complete absorption at the end with alcoholic potash, and these served for Experiments II, III, and IV. For Experiment V the Young's Fractional Distillation Column, which happened to be available to us, was used for the bubbling and proved most effective for the purpose.

Experiment I, September 3rd, 1916.—*Breaking Down House at* ——.— This experiment is really given as a control to the others to indicate that if there were a large amount of T.N.T. dust in the air the apparatus as arranged would absorb and show it. The inlet was placed near a receiving bin at the foot of a leaky shoot where there was abundance of visible dust. No worker in the room would breathe as much as this, but this defect made the room about the dustiest we have seen in any T.N.T. factory. All the workers in this room wore respirators for comfort's sake, but there had never been any cases of toxic jaundice amongst them, nor any excess of minor T.N.T. illness. Their work was mechanical and did not involve much handling.

A volume of 1,633 litres of air was drawn through in twenty minutes. The total solid in the water at the end was dried and weighed and found to be 0·18 gramme; from this was extracted by weighing 0·05 gramme of T.N.T. In the mouthpiece there was dust weighing 0·26 gramme, calculated by the above ratios to contain $\frac{1}{18}$ of T.N.T. or 0·07 gramme of T.N.T. So that 1,633 litres of air at this point contained 0·05 + 0·07 gramme = 0·12 gramme of T.N.T.

Tidal air of adult man at rest	= 0·3 × 18 litres per minute = 324 litres per hour.
Add 50 per cent. for exercise and air breathed per hour	= 486 litres.
So that air breathed in 10½ hours' shift	= 5,103 litres.
And from above determination of amount of T.N.T. in air the maximum amount of T.N.T. breathed by a worker who had his mouth opposite this leak in the shoot would be	$= 0{\cdot}12 \times \frac{5103}{1633}$ = 0·37 gramme.

No worker was in this situation, and this preliminary experiment only serves to show that the apparatus will show dust when present.

Experiment II, September 20th, 1916.—*No. 2 Shop, F.*—Four girls in shed pressing amatol blocks. A fatal T.N.T. case had occurred in this

used. The inlet was placed within a foot of the head of a girl serving beside the box of powder, and equally exposed to dust.

A volume of 550 litres was drawn through; the water was dried off, and the weight of solid matter, i.e. amount of dust in 550 litres, was found by weighing to be 0·005 grammes; the amount of T N T in this, as shown by ether-alcohol extraction in Experiment III, was *nil*, i.e. was less than $\frac{12}{20}$ of 1 per cent., so that the amount of T N T in 550 litres of air was less than 0·021 grammes.

Volume of air breathed in one hour, according to calculations in Experiment I (above) = 495 litres (making no deduction for sex).

Volume of air in 7½ hours shift = 7½ × 480 = 3645 litres.

Therefore maximum amount of T N T absorbable from the air = 0·0021 × $\frac{3645}{550}$

= 0·014 grammes.

Experiment III. September 21st, 1916.—Same Shed as Experiment II.—A volume of 3,676 litres drawn through as in the last from 12·30 to 6·15 p.m.

Weight of dry solid in water = 0·020 grammes.

From this T N T extracted by ether, filtered, evaporated, weighed = 0·012 grammes.

Air calculated as in Experiment II breathed in 7½ hours = 3,645 litres.

Therefore maximum amount of T N T available for absorption from air = 0·012 × $\frac{3645}{3676}$

= 0·012 grammes.

Experiment IV. September 22nd, 1916.—Made in same shed adjoining that used for Experiments II and III.—A volume of 8,000 litres drawn through in a total period of 168 minutes, divided into the following periods:—

3.37 p.m.	till	4.7 p.m.	
4.15	,,	4.45	,,
5.5	,,	5.23	,,
6.25	,,	6.55	,,
7.5	,,	7.35	,,
8.3	,,	8.30	,,

The object in thus spacing the time at which the apparatus was run was that a fair sample of the whole shift period might be obtained. The longer break at 5.23 p.m. till 6.55 p.m. is on account of the tea interval.

Weight of total solid matter dust in 8,000 litres = 0·043 grammes.

The proportion of T N T in this was $\frac{12}{20}$ so that the amount of T N T in the dust of 8,000 litres = 0·015 grammes.

Volume of air breathed during 7½ hours' shift = 3,645 litres.

Therefore maximum amount of T N T available from air during shift = 0·015 × $\frac{3645}{8000}$

= 0·0042 grammes.

The average maximum available from all during shift, given by Experiments II, III and IV, is therefore .011 milligrammes or .011 grammes.

Experiment V.—Estimation of Amount of Dust and Fumes in Air in the Melt House at National Shell Factory, Barking.—The air was drawn by means of a vacuum apparatus already referred to in the Melt House through an absorbing apparatus, containing, in a set of bulbs and a fractional distillation apparatus successively joined, and then through a measuring

meter (*see Sketch*). The completeness of absorption was shown by failure of the alcoholic potash test in a glass tube placed between bulbs and meter.

The apparatus ran for total of 8 hours 9 minutes.
Air passed through .. .. = 8,427 litres.
Average rate .. .. = 17·2 litres per minute.
Tidal air of healthy adult man .. .. = 300 c.c. per respiration.
Therefore, air breathed per minute at rest = 300 × 18 respirations.
= 5,400 c.c.
Therefore, air breathed in 9½ hours .. = 3,078 litres.
Add 50 per cent. for exertion :—
Air breathed in 9½ hours' work .. = 4,500 litres approximately.

RESULTS.

1. *T.N.T.*—
Weight of T.N.T. in 8,427 litres of air .. .. = 0·011 gramme.
Therefore, weight of T.N.T. in 4,500 litres of air .. .. .. = $0{\cdot}011 \times \frac{4500}{8427}$
$= 0{\cdot}011 \times 0{\cdot}534$.
Maximum T.N.T. breathed in 9½ hours' work under cylinders .. = 0·0061 gramme.

2. *Ammonium nitrate.*—Trace, unweighable.

3. *Nitrite.*—The Griess Ilosway test only gave a reaction corresponding to 1 part in 150,000 $NaNO_2$.
This was in total water of 65 c.c.
Therefore, nitrite .. .. = 0·00043 gramme as $NaNO_2$.
Nitrous fumes .. .. = 0·0029 gramme as HNO_2.
A negligible quantity.

NOTE.—This experiment shows that the maximum amount of T.N.T. possible of absorption by mouth and nose during a 12 hours' shift is only 0·0061 gramme.

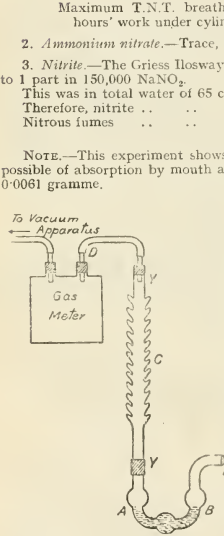


Diagram of apparatus used for the estimation of T.N.T. dust and fumes in the air near the cylinders in the Melt House. The suction was obtained from a vacuum apparatus present in the Melt House. The amount of air passing through was measured by means of the gas-meter.

On starting the suction, the current of air forced water (previously placed in the U-tube to about the level AB) up in the left limb of the U-tube, and the suction force was adjusted so that the spray reached to C or a little higher. All dust and any water-soluble gas were caught by the water. Water was added from time to time to make up for loss by evaporation.

Efficiency of extraction of all T.N.T. from the air was proved by testing the inside tube D with alcoholic potash at the end of the experiment; it was found absolutely free from T.N.T.

yy is a Young's fractionating column.
E is the air inlet, diameter 1 cm.

APPENDIX C.

Amounts of T N T. absorbed under various Experimental Conditions.

This appendix shows in comparative form the results from between three sets of observations—(1) the amount of T N T. absorbed from the workshop air by inhalation and swallowing by breath and nose, the skin of the hands being completely protected; (2) the average available amount in the air shown by the experiments recorded in Appendix D; and (3) the amounts appearing in the results of intentionally swallowing the like quantities but carefully keeping away from the workshops.

As will be seen, the three sets of results are satisfactorily close and so form checks upon one another.

I.—The average available T N T. in the air of the sheds in the amount of air breathed by a worker, as shown by Experiments II and III of Appendix B, is 0·013 grains.

II.—For a period of some days, T A W. and G A W. swallowed daily after breakfast approximately this amount, T A W. taking 0·010 grains and G A W. taking 0·015 grains, and both experimenters during the period refrained carefully from going near the workshops or any source of T N T. absorption.

The results were as follows:—

Reactions in T A W. Dose 0·010 grains.

Date.	Time of Dosage.	Reactions.
Oct. 1918	5 p.m. (at tea). 10 mg.	Oct. 1918.—At 7 p.m. no [illegible] 8 p.m. 1+. 9 p.m. 1. 10 p.m. 1+. 11 p.m. 1+. Oct. 19th.—12 45 a.m., 2. 8·45 a.m. 1+.
„ 1918	— „ „ „	Oct. 19th.—11 15 a.m., nil. 7 10 p.m. 1+. 8 20 p.m., 1. 10 15 p.m. nil.
„ 1918	11 11 15 p.m. „	Oct. 20th.—8 30 a.m. no reaction; Oct. 21st.—12 30 a.m. 1+. 10 a.m. 1.

Reactions in G A W. Dose 0·015 grains.

Date.	Time of Dosage.	Reactions.
Oct. 1918	5 p.m. (at tea). 15 mg.	Oct. 19th.—At 8 p.m. nil. 9 p.m. nil. 10 p.m. nil. 11 p.m. 1. Oct. 19th.—At 12 45 a.m. 1.
„ 1918		Oct. 19th.—At 9 15 a.m. nil. 5 30 p.m. nil. 7 30 p.m. nil. 8 20 p.m. 1. 10 15 p.m. 1+. Oct. 20th.—12 30 a.m. 1+. 1 a.m. nil.
„ 1918	11 11 15 p.m. 10 mg.	Oct. 20th.—At 8 30 a.m. no [illegible] Oct. 21st.—At 12 a.m. 1. 10 a.m. 1.

Note.—Observe that the reaction reaches its maximum about five or six hours after taking the dose, and that the reaction is usually over within twelve hours. It is to be noted in the case of E. M. and M. G. I. that

work accompanied by mouth and nose absorption in small amount went on until 10 p.m. each day, and that the morning urine is a mixed sample of a secretion period from midnight till about 8 a.m. The most important sample in their cases to observe is accordingly that immediately before resuming work at 2 p.m. daily. These figures run for B. M. as follows :— Thurs., v.f.t. ; Fri., v.f.t. ; Sat., 1 ; Sun., f.t. For M. G. F. the corresponding intensities are—Thurs., nil ; Fri., nil ; Sat., f.t. ; Sun., nil. Thus, with the exception of B. M. on the Saturday, the urine was practically clear each day before resuming work.

III.—At the same period B. M. and M. G. F., with their hands completely protected, but wearing no respirators to stop absorption of any T.N.T. in the air, carried on the ordinary work of the workshop.

The results were as follows :—

Reactions in B. M.

Date.	Period of working.	Reaction, and time of taking it.
Mon., Oct. 16th	2–10 p.m.	Oct. 16th—8 a.m., nil ; 5.45 p.m., v.f.t. ; 11.50 p.m., 1. Oct. 17th—8 a.m., 1- ; 1 p.m., f.t.
Tues., ,, 17th	Breakdown	No work done.
Wed., ,, 18th	4–10 p.m.	Oct. 18th—8 a.m., 1- (?) ; 3 p.m., v.f.t.
Thurs., ,, 19th	2–10 p.m.	Oct. 19th—1 a.m., 1 ; 8 a.m., 1 ; 1 p.m., v.f.t. ; 5.30 p.m., t. ; 10 p.m., 1- ; midnight, 1-.
Fri., ,, 20th	2–10 p.m.	Oct. 20th—8 a.m., 1 ; 1 p.m., t. ; 1.40 p.m., v.f.t. ; 5.30 p.m., f.t. ; 10.30 p.m., 1-.
Sat., ,, 21st	2–10 p.m.	Oct. 21st—1 a.m., 1 + ; 9 a.m., 1 ; 2 p.m., 1 ; 5.30 p.m., f.t. ; 11.30 p.m., 1-.
Sun., ,, 22nd	No work	Oct. 22nd—8.30 a.m., 1- ; 3 p.m., f.t.

Reactions in M. G. F.

Date.	Period of working.	Reaction, and time of taking it.
Mon., Oct. 16th	2–10 p.m.	Oct. 16th—8 a.m., nil ; 5.45 p.m., nil ; 11 p.m., t.
Tues., ,, 17th	Breakdown	No work done.
Wed., ,, 18th	4–10 p.m.	Oct. 18th—11.45 p.m., t.
Thurs., ,, 19th	2–10 p.m.	Oct. 19th—9 a.m., 1 ; 1 p.m., nil ; 5.30 p.m., v.f.t. ; 11 p.m., 1.
Fri., ,, 20th	2–10 p.m.	Oct. 20th—9 a.m., 1 ; 12.30 p.m., nil ; 1.30 p.m., nil ; 5.30 p.m., v.f.t. ; 10.30 p.m., 1.
Sat., ,, 21st	2–10 p.m.	Oct. 21st—9 a.m., 1- ; 1 p.m., f.t. ; 11.45 p.m., f.t.
Sun., ,, 22nd	No work	Oct. 22nd—8.45 a.m., 1- ; 4 p.m., nil.
Mon., ,, 23rd	No work	Oct. 23rd—10.30 a.m., nil.
Tues., ,, 24th	No work	Oct. 24th—9 a.m., nil.

Notes.—The contractions mean as follows :—v.f.t., very faint trace ; f.t., faint trace ; t., trace. Allowing for breaks for tea and undressing, the working period was about seven hours.

APPENDIX D.

Experiments on Protection of the Hands.

Experiments devised to afford protection to the skin have been carried out on the lines described in the text. The results are given in the following protocols:—

I.—Experiment upon the Washing of the Hands by a T.N.T. Solvent (Xylenes).

The first column gives the amount of T.N.T. still in the system on returning to T.N.T. work after a rest period on other work. The columns marked "On" T.N.T., Xylene in use all this time" show the urinary reactions during the period "on" T.N.T. work. The remaining columns show an after period; first, when "off" T.N.T. work, and, secondly, when "on" T.N.T. work but without any washing during this period.

Name.	I. Before Xylene washing, 7th & 8th Jan., 1917, Sun. and Mon.	II. "On" T.N.T. Xylene in use all this period. Jan. 11, Th.	Jan. 17, W.	Jan. 18, Th.	Jan. 19, F.	Jan. 21, Su.	Jan. 27, S.	III. "Off" T.N.T. work. No Xylene washing. Nature of job in brackets. Feb. 9th	IV. "On" T.N.T. No Xylene washing. End of "on" period. Feb. 4th, 1917.
C	t	—	—	—	l	—	l	—	—
F.	v.f.t.	—	l	—	—	—	2	—	—
G	l	3	—	—	—	—	2	f.t. (fuses)	—
H. (1)	l	l	3	—	l	2	3	f.t. (fuses)	2
H. (2)	f.t.	l						—	4
J	3	l	3	—	3	3	3	l (fuses)	4
M. (1)	l	t	t	v.f. t.	v.f. t	v.f. t	—	—	—
R.	2	—	l	—	—	—	—	—	—
S. (1)	2	l	—	—	—	—	—	—	—
S. (2)	l	l	l	—	3	—	3	l (black powder)	3
T (1)	3	—	—	—	l	—	—	—	—
T (2)	2	t	—	—	f.t.	—	3	—	—
W (1)	l	2	—	—	—	—	—	—	—
W. (2)	l	4	—	—	—	—	—	—	—
W. (3)	0	t	t.	—	—	—	—	—	—
M. (2)	—	—	l	—	3	l	—	—	2
Totals	19	15	11	—	13	—	20	—	15
No. of samples	18	11	8	—	9	—	8	—	5
Average intensity	1·2	1·4	1·4	—	1·4	—	2·5	—	3

Notes.—The above table illustrates many points. The large number of blanks in it shows the difficulties of obtaining urinary specimens. The considerable figures in the first column show the difficulties of obtaining good "alternation." If good "alternation" had been attained these samples ought to have been clear. The rise in the figures in the nineteen days "on" shows the inefficiency of the Xylene washing as a protective

The column headed III shows the good results of the period "off" T.N.T., but the number of samples is too small for fair judgment; but Column IV shows the additive effect of the period "on" T.N.T. A large number of controls were carried out upon girls not using the "Xylenes" wash during the actual experiment (Column II, Jan. 11th till Jan. 27th); the average of these gave 1·3, a figure almost identical with that of the girls using the wash—certainly no worse.

II.—The Casein-Varnish Experiment.

Twelve girls were started on 28th Feb., 1917, with an application of casein-varnish twice daily to hands and face, before starting work. The results of the urine tests in these twelve, or in as many of them as gave samples, may be summarised as follows:—

Date.		Samples.	Average reaction.
28.2.17	Before varnish and after 2 days on T.N.T.	10	1·2
10.3.17	After " " 2 weeks on "	10	2
19.3.17	" " " 1 week off "	8	1·1
30.3.17	" " " 11 days on "	7	1·1
28.4.17	" " " 2 weeks on "	6	0·3

The full table of results is appended.

Number.	28/2. 2 days on T.N.T.	10/3. 2 weeks on T.N.T.	19/3. 1 week off T.N.T.	30/3. 11 days on T.N.T.	28/4. 2 weeks on T.N.T.
1	—	2	2	—	v.f.t.
2	1	v.f.t.	1	3	v.f.t.
3	f.t.	1	—	f.t.	0
4	2	4	—	—	—
5	f.t.	1	f.t.	v.f.t.	f.t.
6	2	4	3	1	—
7	—	2	1	2	t.
8	1	—	—	—	—
9	2	2	f.t.	—	—
10	2	2	1	—	—
11	1	—	—	—	—
12	1	2	0	v.f.t.	v.f.t.
Totals ..	12	20	9	8	2·0
Samples ..	10	10	8	7	6
Average reaction ..	1·2	2·0	1·1	1·1	0·3

The letters f.t. mean faint trace; v.f.t. very faint trace; and t. trace.

The appearance of the hands and faces of these six girls, who had carefully used the varnish throughout the period of two months, tallied with the low results in the urines. The highest of the six is only a "trace." This furnishes another proof of the value of skin protection; this trace probably represents the amount swallowed.

The numbers are, of course, too small to draw final conclusions. Large scale experiments have been arranged at other factories.

APPENDIX E

Protocols of Experiments on Administration of T N T and other Nitro-Compounds to Animals

I.—Experiments on T N T with Lethal Results.

A.—Animals showing Liver Lesions.

Experiment I.—May 2nd, 1916.—Rabbit weighing 2,030 grammes given 1·5 gram powdered T N T by mouth at 11·30 a.m. May 3rd urine is dark red coloured.

This dose of 1·5 grm. was repeated on May 3rd, 4th, 5th and 6th (Saturday), and the animal was found dead on 8th (Monday). The urine was dark red in colour throughout the period, and the faeces contained free T N T. After the third dose it appeared unwell and refused food. On May 5th the weight had dropped to 1,850 grammes, and at death it was 1,765 grammes.

The tissues contained no free T N T. The organs were examined by Dr. H. M. Turnbull, who reported that the liver showed large areas of necrosis and fatty degeneration in centres of lobules.

Experiment II.—May 8th, 1916.—Rabbit weighing 2,270 grammes given 1·5 gram of powdered T N T by mouth and placed in metabolism cage at noon. The urine showed the deep red colour within hours feeding. This dose was repeated on May 9th and May 10th, and the animal was found dead on May 11th; weight at death, 2,020 grammes. At the P.M. examination there was considerable wasting, showing in subcutaneous fat, perirenal and scrotal fluids, and liver where lobular borders were luminous in yellow. The organs were given to Dr. Turnbull for examination, and his report was that the macroscopical changes in the liver were "conspicuous fatty degeneration of the centres of the lobules of the liver."

Experiment III.—May 15th, 1916.—Rabbit weighing 1,310 grammes given by stomach 2 grammes of pure T N T. Died two days later. The tissues, including portions of liver lobules and bile duct, were bile stained. The bladder was distended and contained blood-stained urine. The organs were extracted with hot alcohol, and the extracts were tested for T N T with negative results.

B.—Animals showing no Liver Lesions.

Experiment I.—*May 8th, 1916.*—Rabbit, weighing 2,320 grammes, given by mouth 0·6 gram of the pink material* obtained by the action of alcoholic potash. No obvious results seen. The dose of 0·6 gram was repeated on the following dates:—May 9th, 10th, 11th, 12th, 13th and 15th. The animal lost weight as follows:—May 12th, 2,220 grammes; May 13th, 2,000 grammes; May 17th, 1,905 grammes; May 20th, 1,700 grammes; May 24th, 1,430 grammes. Poisoning ceased June 13th, weight 1,275 grammes. At P.M. examination no lesions were seen in any of the organs, but all fat deposits had disappeared and there was great emaciation. This loss of weight is characteristic of animals which survive for any appreciable time on heavy doses of T N T, and is met with in other doses (see Section II of this Appendix). It is interesting that similar results, following on absorption of chemical plants, are recorded from coal workers in fast-rising classes.[1]

Experiment II.—*May 8th, 1916.*—Rabbit weighing 2,130 grammes, given tuberculin (strength 5 c.c. of 0·5 per cent. solution of pink precipitate of T N T in water). No obvious effects were noted, this dose being 0·025 gram. The dose was repeated as follows:—May 13th, 11th, 12th, 15th, 17th, 20th, 23rd and June 7th. The animal was found dead on June 15th. Nothing but extreme emaciation was observed at P.M. examination. The weight had decreased as follows:—May 12th, 2,125; May 15th, 2,020; May 17th, 1,915; May 20th, 1,830; May 23rd, 1,790; June 7th, 1,380 grammes.

* Manufactured from the same source as commercial explosives for military purposes.

[1] Text illegible.

Experiment III.—May 17th, 1916.—Rabbit, weighing 2,250 grammes, given by mouth 2 grammes of "pure"* granulated T.N.T. (C. & H., P.). The urine was a pale red colour next morning (Thursday, May 18th), and contained a little free T.N.T., otherwise no noticeable effects. On this afternoon the urine passed was very dark reddish brown in colour, and contained free T.N.T., but no bile, albumen, or blood. On Friday morning, May 19th, the animal was found dead; the urine passed during the night contained a good deal of blood. The P.M. examination was made by Dr. Turnbull. The bladder was full of urine, dark red in colour and containing blood but no *free* T.N.T. (at this period Webster's test was not known to us). The tissues were examined for *free* T.N.T. by extraction with hot alcohol, but none could be detected.

This experiment should be compared with one on T.N.T. residues separated from crude T.N.T.

Experiment IV.—May 17th, 1916.—Rabbit, weighing 1,660 grammes, given by mouth 0·5 gram of "pure" T.N.T. without obvious symptoms. This dosage of 0·5 gram was repeated by mouth on the following dates, the drug being enclosed in gelatine capsules:—May 19th, 22nd, 24th, 26th, 29th, 31st and June 2nd. This makes in all eight doses of 0·5 gram repeated at short intervals, totalling 4 grammes. The animal died on June 5th. The P.M. examination showed no macroscopic liver lesions. The liver was rather small, and dark brown in colour. The kidneys were somewhat swollen. The urine contained blood and casts, but no free T.N.T.

The body weight shows the characteristic decline of repeated doses of these compounds at this level, as follows:—May 17th, 1,660; May 22nd, 1,670; May 29th, 1,320; June 5th (dead), 987 grammes.

Experiment V.—May 22nd, 1916.—A small kitten, weighing 500 grammes, was given by mouth 0·5 gram of "pure" T.N.T. The animal died the following day. At the P.M. examination the liver was pale in colour, the kidneys swollen and injected, and yellow coloured at outer part of cortex, the pleuritic and pericardial fluids were increased in amount and greenish-yellow in colour as if there had been slight icterus present.

No free T.N.T. was found in liver, kidneys, urine, brain, bowel contents, stomach contents, or heart muscle.

Experiment VI.—May 22nd, 1916.—Another kitten on this date was given by mouth 0·25 gram of "pure" T.N.T., and on the following day another 0·25 gram of the same drug. This latter dose was vomited up two hours later, and the vomitus contained T.N.T. The animal recovered after being ill, and in the five days after administration its body-weight fell from 530 to 450 grammes.

Experiment VII.—May 24th, 1916.—Cat, weighing 2,170 grammes, given by mouth, in gelatine capsules, 1 gram of the pink precipitate of T.N.T. The animal was found dead next morning with rigor mortis established. At the P.M. examination the liver surface was pale over large areas, and lobulation was very distinct. The stomach contained dark coloured fluid in which the T.N.T. compound was present, and this extended down the small intestine for about 15 inches (*i.e.* about one-third its length). The kidneys were swollen and much congested, but the cortex was pale in colour. There was no urine in the bladder, but a small volume passed about one hour after the administration of the T.N.T. gave no reactions for free T.N.T. There was also absence of T.N.T. in liver and kidneys. The lungs were greyish-brown in the greater part; pink in smaller areas. This, with the previous experiments, demonstrates that the pink substances formed by the action of T.N.T. on alkalies are

* The expression "pure" T.N.T., as used here, means T.N.T. commercially purified. It still contains small percentages of β and γ tri-nitro-toluenes, and of the three isomeric di-nitro-toluenes. None of these, however, is appreciably more poisonous than tri-nitro-toluene.

not innocuous, but have about the same intensity of lethal action as T.N.T. itself, and like the mother substance are more lethal to cats than to rabbits.

Experiment VIII.—June 14th, 1916.—Rabbit, weighing 1,530 grammes. This animal was given, at intervals of a few days, an intermediate sized dosage of 0·5 gram, to try to produce chronic effects. The weight was taken at intervals, counts made of red blood corpuscles, and estimations of hæmoglobin percentages, with the following results :—

Date and Dosage.	Hæmoglobin Content.	R.B.C. Count.	Weight. Grammes.
1.—June 14th	75·8	7,900,000	1,530
2.—" 16th	75·0	8,400,000	—
3.—" 19th	—	—	—
4.—" 21st	—	—	1,310
5.—" 26th Given 0·5 gram "pure" T.N.T.	58·0	5,200,000	—
6.—" 28th	—	—	1,350
7.—" 30th	65·0	7,400,000	—
8.—July 3rd	65·0	8,400,000	—
9.—" 5th	—	—	—
(Urine, red coloured, shows reactions for T.N.T. but contains no blood.)			
10.—July 6th	63·0	6,300,000	1,390
11.—" 10th Given 0·5 gram pure T.N.T.	—	—	—
12.—" 12th	38	4,500,000	—
13.—" 14th Dead	—	—	1,025

This animal had the relatively enormous weight of six grammes administered in twelve half-gram doses within a period of one month. Note the usual large drop in body-weight, and the reduction in hæmoglobin percentage and number of red blood corpuscles.

Similar blood changes have been observed in other animals, and the matter is now being further investigated.

Experiment IX.—June 16th, 1916.—Rabbit, weighing 1,260 grammes, given by mouth, in gelatine capsules, 2 grammes of the pink precipitate of T.N.T. Next day the animal lies on its side without voluntary movements, is comatose, and has very feeble respiration. Death occurred at 11.45 a.m., about twenty-four hours after administration of the drug.

Experiment X.—July 19th, 1916.—Rabbit, weighing 1,980 grammes, given by mouth one dose of 2 grammes of the pink precipitate of T.N.T. No other doses given.

July 19th, R.B.C. 7,900,000; July 31st, R.B.C. 6,100,000. Weight 1,900 grammes; August 7th, R.B.C. 4,500,000; August 14th, died. By an error, no P.M. examination was made.

Experiment XI.—July 25th, 1916.—Rabbit, weighing 1,100 grammes, given 2 grammes "pure" T.N.T. by mouth at 11 a.m.; put in a metabolism box, and passed urine about 5 p.m. The urine tested by Webster's test contained the T.N.T. derivative; it did not contain any blood. A sample of blood drawn from the ear at about 3.30 p.m. gave a faint positive reaction with alcoholic potash. The animal was dead next morning. A sample of urine passed during the night contained modified T.N.T. but no blood.

At the P.M. examination no macroscopic changes in any of the organs was observed. The bladder contained a small amount of dark-coloured urine, which contained the T.N.T. product but no blood.

The several organs were tested by extracting with hot alcohol and testing for T.N.T. in the alcoholic extract, with the following results :— Liver, negative ; kidney, negative ; heart, negative ; blood, negative ; lungs, a distinct purple reaction of unchanged T.N.T. ; stomach contents, a large amount of unchanged T.N.T. ; brain tissues, negative ; intestinal contents, a little unchanged T.N.T. ; bronchial mucous, reaction of unchanged T.N.T.

Experiments on White Rats.—The prolonged experiments (*a*) in the respiratory chamber and (*b*) in the workshop over the melting pans, had shown that air-dust or vapour taken in by mouth and nose had produced no ill results in white rats. In the following experiments the " pure " T.N.T. used in the workshops was dusted over the cages or vessels in which the animals were kept, so that they trod in it and also doubtless licked some off their fur.

Experiment I.—Started March 8th, 1916, *ended fatally March 13th,* 1916.—Kept a white rat in a large glass beaker, mounted on a layer of felt to keep warm. The beaker was dusted over the bottom with fine " pure " T.N.T. powder. The rat's paws and the abdominal fur, as well as the floor of the beaker showed, in a few hours, the characteristic pink of the reaction given by unaltered T.N.T. with alkaline alcohol. This animal was fed daily in the beaker, and the food was also contaminated with T.N.T. The animal was very ill on March 11th, and was changed over into a clean wooden cage provided with straw. Death occurred on March 13th ; the weight had fallen from 68 grammes at start to 50 grammes at death. At the P.M. examination the liver looked pale coloured and patchy on the surface. The intestine contained a dark-brown coloured material, looking like altered blood, but giving no hæmin test ; no hæmorrhagic areas could be made out.

Experiment II.—Started March 8th, moribund and killed March 11th, 1916.—This animal was fed in a separate chamber so that food did not become contaminated with T.N.T., and was then transferred to a beaker which had been dusted over with T.N.T., as in the previous experiment. On the following day the paws and body were bright pink in colour, and urine passed in the beaker was a bright pink, but it was thought then that this colour might have developed by the urine coming in contact with T.N.T. on the floor of the beaker. The animal was moribund on March 11th (Saturday), and was then killed. The only abnormality found was a brown material in patches on the mucosa of the stomach. The brown was not due to T.N.T., and also did not give the hæmin test.

Experiments III and IV.—Started March 10th, ended fatally March 15th.—A 10 per cent. emulsion of " pure " T.N.T. was made in butter, and this was mixed with bread and fed to two white rats. The animals rapidly fell ill, and both died on March 15th. The P.M. examination showed in both cases dark purple coloured intestinal contents ; these, after boiling in alcohol, decanting and adding alkaline alcohol to the alcoholic extract, showed the deep purple colour of the T.N.T. test. The bladder of one contained a quantity of urine which was a bright pink even in the bladder, so proving that the pink colour seen in previous experiments was not due to external contamination but was really formed *intra vitam.* The livers were abnormally dark in colour, and on extracting with hot alcohol the alcoholic extract gave a markedly strong purple with alkaline alcohol. The same result was obtained with heart-blood, and the tissue of the lungs and brain, and kidney.

II.—Experiments with Non-Lethal results, and on Effects of Respiring Fumes and Dust.

A.—Laboratory Experiments on Effects of Breathing Fumes of Crude T.N.T.

The animals were placed for these experiments in a respiratory chamber similar in design to that described by Edie, Moore, and Roaf (*Bio-chemical*

Journal, Vol. V., p. 341, 1910). The capacity of the chamber was about 50 litres. A water pump sucked air through at the outlet tube, and to the air-inlet tube of the chamber a flask fitted with a stopper and two tubes in the manner of a wash bottle was attached. This flask contained either crude or re-crystallised T.N.T., and was placed upon a steam bath so that it was kept at a temperature of 100° C. This is about 20° C. over the melting point of T.N.T., and as warm as any molten T.N.T. in factories to the fumes from which workers might be exposed. A day or two after the apparatus had been running thus with animals in the chamber, crystals of T.N.T. began to appear in the outlet tube, showing that the warmed air drawn over the hot molten T.N.T. had carried a good supply of vapour or fume into the chamber which condensed on the cold exit tube.

Experiment I.—*August 20th, 1915.*—Two guinea pigs, weighing respectively 445 and 335 grammes, were placed in the chamber and exposed for seven hours daily from Monday till Friday, three hours on Saturdays, and left free on Sundays. The experiment was kept up for sixteen working days, and there was no observable effect upon the animals, which appeared at the end quite well, ate well, and slightly increased in weight during the experiment, of which the details are as follows:—

Date.	Hours in Respirator Chamber.	Body weights.	Grams T.N.T. added to flask, to make good loss by evaporation.
Fri., Aug. 20th, 1915	10 a.m.—5 p.m.	445, 335	5 grammes.
Sat., „ 21st, „	10 „ —1 „	—	—
Mon., „ 23rd, „	10 „ —5 „	—	5 grammes.
Tues., „ 24th, „	10 „ —5 „	—	5 grammes.
Wed., „ 25th, „	10 „ —5 „	—	—
Thurs., „ 26th, „	10 „ —5 „	—	—
Fri., „ 27th, „	10 „ —5 „	—	—
Sat., „ 28th, „	10 „ —1 „	—	—
Mon., „ 30th, „	10 „ —5 „	—	—
Tues., „ 31st, „	10 „ —5 „	—	—
Wed., Sept. 1st, „	10 „ —5 „	—	—
Thurs., „ 2nd, „	10 „ —5 „	—	10 grammes.
Fri., „ 3rd, „	10 „ —5 „	456, 340	—
Sat., „ 4th, „	10 „ —1 „	—	—
Mon., „ 6th, „	10 „ —5 „	—	—
Tues., „ 7th, „	10 „ —5 „	—	—

Experiment II.—*August 26th, 1915.*—Two other guinea pigs were put in another respiratory chamber on Thursday August 26th. One of these died and was removed from the chamber on Friday September 2nd. A P.M. examination was made and it was shown that T.N.T. poisoning had nothing to do with the death which was due to a streptococcal pneumonia and intestinal inflammation. This was replaced by a fresh animal and the two pigs occupied the chamber for nine more days. No ill effects were noted in either of them and neither lost appetite or diminished in weight.

Experiment III.—*September 6th, 1915.*—Four white rats were then placed in the respiratory chamber and the crude T.N.T. in the flask was replaced by "pure" T.N.T. purified by successive by-passing the "crude" commercial product from alcoholic alcohol. The results were similar, that is to say entirely negative, the animals showing no toxic or injurious action.

B.—Laboratory Experiments on the Effects of Breathing the Dust and Vapours of T.N.T.

A rabbit was daily placed in a box used for administering drugs by the mouth, so that the head only projected out at the end of the box

A larger box, about 18 inches square at the ends and about 2 feet long, had a round hole made at one side against which the end of the smaller box containing the rabbit might be placed so that the animal's head projected in a fairly fixed position into the large box. At the opposite side of the large box a pipe led in which was attached to a rotary air fan by means of which a strong current of air could be blown through the pipe into the box. A glass rod was fixed horizontally a few inches from the point of entry of this air inlet, and a thin muslin bag filled with " pure " T.N.T. was hung by a thread so that it touched this glass rod when at rest. When the fan was worked this bag was blown about, and kept knocking incessantly against the glass rod, so shaking out T.N.T. dust.

A piece of blotting paper, moistened with alkaline alcohol and held opposite the hole in the large box, soon became covered over with pink spots where T.N.T. dust had landed upon it. Also, the rabbit's head, after an hour's exposure here, showed dusty all over. A slight corneal inflammation appeared after a week's experimentation, but even at the end of a long period of exposure there was no general T.N.T. effect whatever.

Experiment I.—Rabbit weighing 1,670 grammes exposed to T.N.T. dust-box as above described, as follows :—May 23rd, 1916, exposed for one hour (11.55–12.55) ; an exposure of one hour given on May 24th, 25th, 26th and 29th. Again exposures made of one hours' duration on May 30th and 31st and June 1st, 2nd, 5th, 6th, 7th, 8th, 14th, 15th, 16th, 19th, 20th, 21st, 22nd, 26th, 27th, 28th, and for two hours on June 29th and two and a half hours on June 30th.

The experiment was discontinued at this point on account of keratitis from the dust, and as no general effects appeared to be arising from the exposure.

C.—Workshop Experiments on the Effects of Exposing Unprotected Animals to Fume and Dust over melting pans for T.N.T.

These experiments were carried out at W. A., and the fume and dust must be regarded as in excess of anything to which workers would be exposed.

Experiment I.—Started October 4th, 1915, ended December 6th, 1915. —Four guinea-pigs exposed in two pairs in two T.N.T. melt houses, These animals remained in good health for the whole period of two months. when one died suddenly and the other three were taken ill. These other three also died, although removed to the laboratory, but the P.M. examination showed that death in all four cases was due to an infection of a pneumonic type, and unconnected with T.N.T. poisoning. This epidemic gave us great trouble amongst guinea-pigs all this winter, and also put a stop to several of our prolonged experiments in the laboratory with sub-lethal doses of T.N.T. Fortunately it did not set in until our experiments on exposure to T.N.T. had lasted sufficiently long to show the points at issue. These four pigs were exposed for eleven hours daily, as described in the text, from October 4th till November 23rd, and taken away to stores at night, the day temperature being about 80°F. On the latter date there being no T.N.T. effects observable, the cages were placed nearer still to the melting pans, and from November 23rd till December 6th the day temperature for eleven hours daily was about 95°F. No visible result followed, and, as stated, the deaths were due to infection.

Experiment II.—Started December 6th, 1915, ended March 20th, 1916.— Four guinea-pigs were exposed for this period, as described in the preceding experiment. One died of a pneumonic infection on March 20th, 1916, having been quite well until two days previously. There were no signs at the P.M. examination of T.N.T. poisoning, and no T.N.T. reactions could be obtained from urine or tissues. The other three remained healthy, and one had a healthy progeny.

Experiment III.—Started March 22nd, ended June 26th, 1916.—Six young white rats were exposed for this period in the same situation and

conditions. The white fur turned yellow in colour, but the animals remained good healthy and grew to a large size. One was killed and examined; there was nothing abnormal except perhaps a very large accumulation of fat in connection with the liver and kidneys. There was no T.N.T. in urine or tissues. Contrary to the result with experiments on white rats exposed to T.N.T. (see p. 1).

Experiment IV.—Started June 20th, 1916 *ended November 14th, 1916.*—Two rabbits were placed in the same position as were previously occupied by the guinea-pigs and white rats on June 20th, 1916 and the report on November 14th, 1916, from the officer in charge was as follows:—"The two rabbits placed in the rabbit hutch on June 20th, 1916 are still quite healthy, and appear to be unaffected by their exposure to the fumes. They have been regularly fed and watered by their keeper each day, and have been removed to the open during the night."

D. Observations of comparatively small or sub-lethal doses over longer periods.

Experiments on Guinea-pigs.

Experiment I.—Started October 14th, 1915 *ended January 17th, 1916.*—Guinea-pig, weighing at outset 420 grammes, at most 500 grammes, given, by means of pipette, 0·025 gramme of spirit containing T.N.T., every two calendar months for 3 months. Total amount of T.N.T. given 0·075 gramme. All the doses were administered between the interval marking a total of 1·2 grammes of T.N.T. The daily weight of animal was taken as follows:—November 1st, 440 grammes; 3rd, 440; November 10th, 440; November 23rd, 440; December 2nd, 455; December 14th, 440.

November 1st T.N.T. poisoning was noticed for the animal, which is double that of the preceding experiment. The animal died two weeks after the termination of the experiment, and quite confirms the general conclusion.

Experiment II.—Started November 1st, 1915 *ended December 17th, 1915.*—Guinea-pig, weighing 440 grammes at start and 525 grammes

at end, given 0·050 gramme doses, by mouth ; a companion experiment to preceding one. Number of doses, 27 ; total amount, 1·35 gramme. Body-weight, in grammes, November 1st, 1915, 440 ; November 9th, 500 ; November 16th, 459 ; November 23rd, 500 ; December 2nd, 520 ; December 13th, 525.

No poisonous effects visible, and the animal continued well for some weeks afterward.

Experiment V.—Started November 1st, 1915, ended December 15th.—Guinea-pig, weighing 340 grammes at start, 360 grammes at end, was given by mouth doses of 0·075 gramme (*i.e.*, half as much again as two animals in Experiments III and IV) of T.N.T. Total number of doses during interval, 21, making a total of 1·575 grammes of T.N.T. Body-weight in grammes :—November 1st, 340 ; November 9th, 295 ; November 16th, 257 ; November 23rd, 290 ; December 2nd, 362 ; December 13th, 360.

No visible effects ; died later, January 18th, 1916, from pneumonic infection.

Experiment VI.—Started November 1st, 1915, ended December 15th, 1915.—Guinea-pig, weighing 370 grammes at start and 370 grammes at end. Companion experiment to above ; given doses of 0·075 grammes T.N.T. Total number of doses, 21 ; total weight of T.N.T., 1·575 gramme. No visible effects ; died of pneumonic infection four weeks later, on January 12th, 1916.

B.—*Experiments on Rabbits.*

Experiments I and II.—Started October 15th, 1915, *ended December 17th,* 1915.—Two large rabbits were kept during this period at times in metabolism cages, and at times in hutches in animal house, and given frequent doses of 0·100 gramme of T.N.T. by mouth. Rabbit No. 1 weighed at commencement 2,190 grammes, and was given crude commercial T.N.T., while rabbit No. 2 weighed at commencement 2,520 grammes, and was given twice crystallised T.N.T. (re-crystallised from hot absolute alcohol).

Rabbit No. 1 (on crude T.N.T.).—Total number of doses of 0·100 gramme of T.N.T. given during experiment, 37, making a total amount of 3·7 grammes. On December 17th this animal was given 0·300 gramme of crude T.N.T. by mouth, followed by 5 c.c. of 50 per cent. alcohol, thus making a total of 4 grammes of T.N.T. throughout the experiment. No positive results were obtained as a result of this long continued absorption of crude T.N.T. This rabbit, during the period, had administered to it at least six-fold the amount which the average T.N.T. worker could possibly absorb, *by mouth and nose,* from factory air in a similar period.

The following results of weighings at intervals show that the animal throve and increased in weight :—October 15th, 1915, 2,190 ; October 26th, 2,137 ; November 2nd, 2,160 ; November 16th, 2,110 ; November 23rd, 2,250 ; December 2nd, 2,259 ; December 13th, 2,570 ; January 6th, 1916, 2,350 ; January 24th, 2,450.

Rabbit No. 2 (on recrystallised T.N.T.).—Total number of doses of 0·100 gramme of T.N.T. given during experiment, 37, making a total amount of 3·7 grammes. On December 17th this animal was given a single dose of 0·3 grammes, which was not followed by any alcohol. The results throughout were negative, as in the companion experiment with the crude drug, and show that at this level of dosage the rabbit is immune to T.N.T. and also to any admixed impurities in its commercial production. This is interesting because, in regard to action in the body, this animal stands nearer to the action in human beings than any of the other animals experimented upon.

The body-weights of this animal were as follows :—October 15th, 1915, 2,520 ; October 26th, 2,585 ; November 2nd, 2,830 ; November 9th, 2,590 ; November 16th, 2,590 ; November 23rd, 2,740 ; December 13th, 2,970 ; January 6th, 1916, 3,120 ; January 24th, 3,180.

Experiment III.—Started August 23rd, 1916. Discontinued August 28th, 1916. This experiment was instituted to test for skin absorption in the rabbit.

A rabbit weighing 2,080 grammes had the hair clipped off over an area of the back measuring about 14 — 11 cm. Over this two layers of muslin 11 — 8 cm. were tied, and the muslin was saturated with 12 c.c. of olive oil in which 4 per cent. of "pure" T.N.T. had been dissolved, making the amount of T.N.T. applied 1·920 in the skin about half a gramme. The caked muslin was covered on by an adhesive impermeable dressing of silk proofed with a solution of acetate of soluble, and finally bound with Mead's plaster. The surrounding fur was carefully tested for T.N.T. with negative results, to show the animal could obtain none by licking and that there could be no external contamination of the urine. The animal was then placed in a metabolism box to collect urine.

A sample of urine obtained next morning at 11 a.m. was pale coloured and contained no T.N.T. derivatives, but one passed at 4 p.m. was dark amber in colour, faintly acid, and gave the T.N.T. reaction. The dressing on the muslin was removed, and the impermeable dressing reapplied. Next day the T.N.T. reaction was obtained again in the urine. The jaws and tongue of the animal were tested for T.N.T. to exclude licking effects, and gave a negative result. The T.N.T. reaction in the urine was found to persist for a period of four days afterwards.

(c) Experiments on Cats.

Experiment I.—Started November 17th, 1915. ended December 3rd, 1915. A cat, weighing 4·750 grammes, was given by mouth during this interval six doses each of 0·100 gramme of crude T.N.T. No ill results were observed.

Experiment II.—Started May 24th, 1916. Discontinued July 7th, 1916. A cat, weighing 2·650 grammes, was given by mouth 1 gramme "pure" T.N.T. enclosed in gelatine capsules. The animal was very ill on May 25th and vomited for 18 hours afterwards, and refused to have anything to do further. On May 29th it appeared much better but was still very quiet, but weight had fallen to 2·240 grammes. Another gramme of the "pure" T.N.T. was given on June 8th, and did not produce nearly so much effect as the first dose. Another dose of 1 gramme was given on June 16th with a little positive result, weight now 2·530 grammes. The animal was given 2 grammes "pure" T.N.T. on July 4th, and placed in metabolism box to collect urine and faeces, but was extremely sick and vomited for the greater part of the day, so the experiment was discontinued. The animal on July 7th was 2·100 grammes.

III. Experiments with T.N.T. Impurities, and the Mixed and Di-nitro Compounds formed Accidentally in the Commercial Product.

*Experiment I.—*May 16th, 1916.—Rabbit weighing 1,310 grammes given by mouth 2 grammes of T.N.T. residues, obtained in purification of crude T.N.T. (D.M. & Co.). The nature of the drug was found to be much darker than, and contained less T.N.T. Blood was present in the urine on May 19th and May 20th. The animal was examined on May 20th and was killed; the weight had fallen to 1,070 grammes. No macroscopic lesions were noticed at the P.M. examination. This is an enormous dose for a small rabbit yet did not kill for four days. A comparison should be made with Experiment III Section B where an equal dose of "pure" T.N.T. was given to a rabbit of 2,250 grammes, which died in two days. This shows clearly that those impurities or "residues" contained in crude T.N.T. and removed in process of purification of the commercially "pure" T.N.T., are no more poisonous than is the "pure" T.N.T. itself left behind after their removal.

Experiment II.—June 22nd, 1916.—Rabbit weighing 2,510 grammes given by mouth 1 gramme of di-nitro-toluene, viz., that fraction melting at 20–25°C. (L. B. H.); this remains in small percentage in commercially "pure" T.N.T. The animal showed no injurious effects a fortnight later, its body-weight was 2,020 grammes, and no later results followed.

Experiment III.—June 22nd, 1916.—Rabbit weighing 2,010 grammes given by mouth, in gelatine capsules, 1 gram di-nitro-toluene; that fraction melting at 65°C. (L.B.H.). No ill results followed; the body-weight on July 7th was 2,020 grammes, and there were no later results.

Experiments IV and V.—Started December 14th, 1915, *ended January 17th*, 1916.—Two guinea-pigs were given mono-nitro-toluene by mouth—No. 1 received doses of 0·5 cc. and No. 2 doses of 1 c.c.

Guinea-pig No. 1 was given four doses of 0·5 c.c. of *mono-nitro-toluene* on December 14th, 15th, 16th, 17th. No results were observed. The body-weights were December 14th, 390; January 6th, 1916, 340; January 17th, 1916, 330.

Guinea-pig No. 2 was given four doses of 1 c.c. on December 14th, 15th, 16th, 17th. Weights—December 14th, 390; January 6th, 590; January 17th, 620. No ill results.

Experiment VI.—Placed three guinea-pigs in respiratory chamber into which air was bubbled through mono-nitro-toluene, which is fluid at atmospheric temperatures. The animals were subjected to the fumes from mono-nitro-toluene from 10 a.m. till 5 p.m. daily on 15th, 16th, 17th and 18th December, 1915, without showing any effects, and were subsequently kept under observation until January 17th, when they succumbed to the universal epidemic of pneumonic infection amongst the guinea-pigs. Thus, the vapour of the fluid mono-nitro-toluene, which occurs as an impurity in crude commercial T.N.T., is as innocuous *quantitatively* as is T.N.T. vapour itself, and it is only present in the commercial mixture in small amount. The body-weights at start and finish were 400, 250, 370 grammes and 370, 240, 370 grammes respectively.

IV. Experiments with Di-nitro-phenol.

Experiment I.—May 15th, 1916.—Rabbit weighing 1,780 grammes given *by mouth* 1 gram of di-nitro-phenol died the same afternoon, showing strongly marked dyspnœic convulsions. The urine was stained a deep yellow colour.

Experiment II.—May 17th, 1916.—Rabbit weighing 1,935 grammes given, at noon, 0·5 gram of di-nitro-phenol dissolved in water, *by mouth*. The animal died at 2 p.m. next day.

At the P.M. examination the bladder was found distended; the urine was dark coloured and contained D.N.P.; there was no bile present, or blood, albumen or dextrose. The kidneys seemed to be swollen, the stomach wall thick and oedematous, and the intestinal blood-vessels were congested.

Experiment III.—May 22nd, 1916.—Rabbit weighing 2,480 grammes was given *by mouth* 0·1 gram of di-nitro-phenol, and showed no immediate effects. The dose of 0·1 gram was repeated on May 24th, and on May 26th and May 29th doses of 0·2 gram were given, all these doses being administered *by mouth*. The animal was found dead on May 30th. No macroscopic lesions were found in any of the organs.

Experiment IV.—Rabbit weighing 1,450 grammes given *by subcutaneous injection* 0·15 gram of the sodium salt of di-nitro-phenol, dissolved in 3 c.c. of water. The animal died in 30 minutes.

Experiment V.—Rabbit weighing 1,160 grammes given hypodermically 0·05 gram, dissolved in 0·7 c.c. of water. A second 0·05 gram dose was given twenty-four hours later, the animal having survived the first dose, and it died forty-five minutes after receiving this second dose.

The amino derivative of dinitro-phenol was present in the urine the morning after the first dose, but urine tested in the bladder (PM.) gave no reaction. No changes in tissues could be detected.

Experiment VI.—Rabbit, given hypodermically 0·1 gram of dinitro-phenol dissolved in olive oil. The animal died in two and a half hours. The kidneys gave a positive reaction to the test for amino-nitro-phenol.

Experiment VII.—A cat was given, hypodermically, 0·025 gram of dinitro-phenol in 0·75 c.c. of olive oil. One hour later slight cyanosis was observed, and in two and a half hours there was distinct cyanosis. After twenty-four hours a dose of 0·05 gram of dinitro-phenol was similarly given, and two hours later there was dyspnœa and cyanosis. Next day there was no longer dyspnœa but still a slight cyanosis. A third dose, this time of 0·075 gram, was given again hypodermically, and the animal died in two hours. At the P.M. the liver was found mottled on the surface; there were no other abnormalities seen.

Experiment VIII.—*July 27th, 1917.*—Rabbit of 1,980 grammes had applied on a clipped surface of the back a lanoline ointment which had, in the portion used, about 0·2 gram of dinitro-phenol. On the 28th it was noticed that the coat had been disarranged, and the animal had licked off some of the ointment. A second dose of 0·2 gram was given, and the coat fixed firmly. The animal survived both doses.

Experiment IX.—*July 31st, 1917.*—Rabbit of 1,440 grammes had 0·3 gram of dinitro-phenol applied to skin of back. Licking was carefully prevented. Next day at 11 a.m. animal was very ill, and the temperature in the rectum had fallen to 94° F., death followed at 2 p.m. The P.M. examination showed that a large portion had not been absorbed, probably not more than 0·15 gram of dinitro-phenol had been taken up. No methæmoglobin could be detected in the blood, and none of the drug was demonstrable in kidneys, liver or blood.

Experiment X.—*August 3rd, 1917.*—Rabbit of 1,400 grammes given 0·1 gram in lanolin ointment on skin. The animal died during night of August 6th, *i.e.*, after three and a half days. Most of the drug had been absorbed, and at the P.M. examination the liver showed a slight nutmeg appearance.

Experiment XI.—*August 10th, 1917.*—Rabbit of 1,280 grammes given on the skin in lanolin 0·05 gram of dinitro-phenol, with negative results. This was followed by 0·1 gram, and this animal survived this dose also.

These experiments show clearly that this nitro-compound is readily absorbed by the skin, and can easily produce lethal results through that channel alone. That the lethal dose is much smaller than in the case of tri-nitro-toluene, both for cats and rabbits, and that there appears to be a certain factor here also of individual idiosyncrasy. As in the case of T.N.T. there is much more cyanosis in cats than in rabbits, of indeed there is any whatever in this latter animal class.

V. EXPERIMENTS WITH DI-NITRO-NAPHTHOL.

Experiment I.—May 17th, 1916.—Rabbit weighing 2,850 grammes given by mouth 2 grammes of di-nitro-naphthol; no noticeable results followed. This dosage of 2 grammes was repeated by mouth on the following days: May 18th, 19th, 22nd, 24th, 29th. This amounts to six doses of 2 grammes each, making 12 grammes in all, at short intervals. The only noticeable change was a small fall in weight which might have been purely adventitious. The weights were: May 17th, 2,850; May 22nd, 2,850; May 29th, 2,140; *July 7th*, 2,570 grammes. The animal thus completely recovered even with these enormous doses.

Experiment II.—May 31st, 1916.—Cat weighing 2,830 grammes given by mouth 1·95 gram of di-nitro-naphthol in solution (ammonia). No injurious effects of any kind were perceived, and on July 7th, 1916, that is five weeks later, the animal's body-weight was 2,350 grammes.

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